PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 237/14, 401/06, 403/06, 237/18, 409/06, 413/06, 405/06, A61K 31/50, C07F 11/00

A1

(11) International Publication Number: WO 99/10331

(43) International Publication Date: 4 March 1999 (04.03.99)

(21) International Application Number: PCT/US98/16479

(22) International Filing Date: 10 August 1998 (10.08.98)

(30) Priority Data:

08/917,023	22 August 1997 (22.08.97)	US
Not furnished	5 August 1998 (05.08.98)	US

(71) Applicant: ABBOTT LABORATORIES [US/US]; CHAD 0377/AP6D-2, 100 Abbott Park Road, Abbott Park, IL 60064-3500 (US).

(72) Inventors: BLACK, Lawrence, A.; 1173 Tamarack Lane, Libertyville, IL 60048-3647 (US). BASHA, Anwer; 41 Heron Road, Lake Forest, IL 60045 (US). KOLASA, Teodozyj; 118 Walden, Lake Villa, IL 60046 (US). KORT, Michael, E.; 507 N. Green Avenue, Lake Bluff, IL 60044-1520 (US). LIU, Huaqing; 1173 Forums Court #2A, Wheeling, IL 60090 (US). McCARTY, Catherine, M.; 231 Freeman Street, Brookline, MA 02446 (US). PATEL, Meena, V.; Tower 3, Apartment #3703, 605 W. Madison Street, Chicago, IL 60661 (US). ROHDE, Jeffrey, J.; Apartment D-1, 1621 Ridge Avenue, Evanston, IL 60201 (US).

(74) Agents: WARD, Michael, J. et al.; Abbott Laboratories, CHAD 0377/AP6D-2, 100 Abbott Park Road, Abbott Park, IL 60064-3500 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: ARYLPYRIDAZINONES AS PROSTAGLANDIN ENDOPEROXIDE H SYNTHASE BIOSYNTHESIS INHIBITORS

(57) Abstract

The present invention describes pyridazinone compounds which are cyclooxygenase (COX) inhibitors, and in particular, are selective inhibitors of cyclooxygenase-2 (COX/2), COX-2 is the inducible isoform associated with inflammation, as opposed to the constitutive isoform, cyclooxygenase-1 (COX-1) which is an important "housekeeping" enzyme in many tissues, including the gastrointestinal (GI) tract and the kidneys. The selectivity of these compounds for COX-2 minimizes the unwanted GI and renal side-effects seen with currently marketed non-steroidal anti-inflammatory drugs (NSAIDs).

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

ARYLPYRIDAZINONES AS PROSTAGLANDIN ENDOPEROXIDE H SYNTHASE BIOSYNTHESIS INHIBITORS

This application is a continuation-in-part application of U.S. patent application Serial No. 08/917,023 filed August 22, 1997, which was based on provisional application 60/056,733 filed August 22, 1997.

Technical Field

The present invention encompasses novel pyridazinone compounds useful in the treatment of cyclooxygenase-2 mediated diseases. More particularly, this invention concerns a method of inhibiting prostaglandin biosynthesis, particularly the induced prostaglandin endoperoxide H synthase (PGHS-2, cyclooxygenase-2, COX-2) protein.

Background of the Invention

The prostaglandins are extremely potent substances which produce a wide variety of biological effects, often in the nanomolar to picomolar concentration range. The discovery of two forms of prostaglandin endoperoxide H synthase, isoenzymes PGHS-1 and PGHS-2, that catalyze the oxidation of arachidonic acid leading to prostaglandin biosynthesis has resulted in renewed research to delineate the role of these two isozymes in physiology and pathophysiology. These isozymes have been shown to have different gene regulation and represent distinctly different prostaglandin biosynthesis pathways. The PGHS-1 pathway is expressed constitutively in most cell types. It responds to produce prostaglandins that regulate acute events in vascular homeostasis and also has a role in maintaining normal stomach and renal function. The PGHS-2 pathway involves an induction mechanism which has been linked to inflammation, mitogenesis and ovulation phenomena.

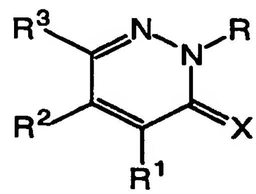
Prostaglandin inhibitors provide therapy for pain, fever, and inflammation, and are useful therapies, for example in the treatment of rheumatoid arthritis and osteoarthritis. The non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, naproxen and fenamates inhibit both isozymes. Inhibition of the constitutive enzyme PGHS-1 results in gastrointestinal side effects including ulcers and bleeding and incidence of renal problems with chronic therapy. Inhibitors of the induced isozyme PGHS-2 may provide anti-inflammatory activity without the side effects of PGHS-1 inhibitors.

The problem of side-effects associated with NSAID administration has never completely been solved in the past. Enteric coated tablets and co-administration with misoprostol, a prostaglandin derivative, have been tried in an attempt to minimize stomach toxicity. It would be advantageous to provide compounds which are selective inhibitors of the induced isozyme PGHS-2.

The present invention discloses novel compounds which are selective inhibitors of PGHS-2.

Summary of the Invention

The present invention discloses pyridazinone compounds which are selective inhibitors of cyclooxygenase-2 (COX-2). The compounds of the present invention have the formula I:



where

X is selected from the group consisting of O, S, NR^4, $N\text{-}OR^a$, and $N\text{-}NR^bR^c$, wherein R^4 is selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, heterocyclic, heterocyclic alkyl, and arylalkyl; and R^a, R^b, and R^c are independently selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, aryl, and arylalkyl;

R is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkylcarbonylalkyl, alkylsulfonylalkyl, alkylsulfonylarylalkyl, alkoxy, alkoxyalkyl, carboxy, carboxyalkyl, cyanoalkyl, haloalkyl, haloalkenyl, haloalkynyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, arylhaloalkyl, arylhydroxyalkyl, aryloxy, aryloxyhydroxyalkyl, aryloxyhaloalkyl, arylcarbonylalkyl, haloalkoxyhydroxyalkyl, heterocyclic, heterocyclic alkyl, heterocyclic alkoxy, heterocyclic oxy, $-C(O)R^5$, $-(CH_2)_nC(O)R^5$, $-R^6\text{-}R^7$, $-(CH_2)_nCH(OH)R^5$, $-(CH_2)_nCH(OR^d)R^5$, $-(CH_2)_nC(NOR^d)R^5$, $-(CH_2)_nC(NR^d)R^5$, $-(CH_2)_nCH(NOR^d)R^5$, $-(CH_2)_nCH(NR^dR^e)R^5$,

$-(CH_2)_nC{\equiv}C-R^7$, $-(CH_2)_n[CH(CX'_3)]_m-(CH_2)_n-CX'_3$, $-(CH_2)_n(CX'_2)_m-(CH_2)_n-CX'_3$, $-(CH_2)_n[CH(CX'_3)]_m-(CH_2)_n-R^8$, $-(CH_2)_n(CX'_2)_m-(CH_2)_nR^8$, $-(CH_2)_n(CHX')_m-(CH_2)_n-CX'_3$, $-(CH_2)_n(CHX')_m-(CH_2)_n-R^8$, and $-(CH_2)_n-R^{20}$,

wherein R^5 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, haloalkenyl, haloalkynyl, heterocyclic, and heterocyclic alkyl;

wherein R^6 is alkylene or alkenylene, or halo-substituted alkylene halo-substituted alkenylene;

R^7 and R^8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclic, and heterocyclic alkyl;

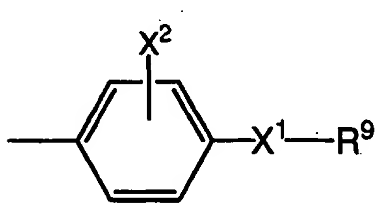
R^{20} is selected from the group consisting of alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkenyl, aryl, heterocyclic, and heterocyclic alkyl;

R^d and R^e are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclic, and heterocyclic alkyl;

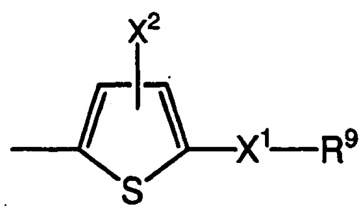
X' is halogen;

n is from 0 to about 10, and m is 0 to about 5;

at least one of R^1, R^2 and R^3 is



or



where X^1 is selected from the group consisting of $-SO_2-$, $-SO(NR^{10})-$, $-SO-$, $-SeO_2-$, $PO(OR^{11})-$, and $-PO(NR^{12}R^{13})-$,

R^9 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, amino, $-NHNH_2$, $-N{=}CH(NR^{10}R^{11})$, dialkylamino, alkoxy, thiol, alkylthiol, protecting groups, and protecting groups attached to X^1 by an alkylene;

X^2 is selected from the group consisting of hydrogen, halogen,.alkyl, alkenyl, and alkynyl;

R^{10}, R^{11}, R^{12}, and R^{13} are independently selected from the group consisting of hydrogen, alkyl, and cycloalkyl, or R^{12} and R^{13} can be taken together, with the nitrogen to which they are attached, to form a heterocyclic ring having from 3 to 6 atoms.

The remaining two of the groups of R^1, R^2, and R^3, are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, halogen, alkyl, alkenyl, alkynyl, alkylamino, alkenyloxy, alkylthio, alkylthioalkoxy, alkoxy, alkoxyalkyl, alkoxyalkylamino, alkoxyalkoxy, amido, amidoalkyl, haloalkyl, halolkenyloxy, haloalkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkenylalkoxy, cycloalkylalkoxy, cycloalkylalkylamino, cycloalkylamino, cycloalkyloxy, cycloalkylidenealkyl, amino, aminocarbonyl, aminoalkoxy, aminocarbonylalkyl, alkylaminoaryloxy, dialkylamino, dialkylaminoaryloxy, arylamino, arylalkylamino, diarylamino, aryl, arylalkyl, arylalkylthio, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, heterocyclic, heterocyclic alkyl, heterocyclic(alkyl) amino, heterocyclic alkoxy, heterocyclic amino, heterocyclic oxy, heterocyclic thio, hydroxy, hydroxyalkyl, hydroxyalkylamino, hydroxyalkylthio, hydroxyalkoxy, mercaptoalkoxy, oxoalkoxy, cyano, nitro, and -Y-R^{14}, wherein Y is selected from the group consisting of -O-, -S-, -C(R^{16}) (R^{17})-, -C(O)N$R^{21}R^{22}$-, -C(O)-, -C(O)O-, -NH-, -NC(O)-, -N=C $R^{21}R^{22}$, N- $R^{21}R^{22}$, and -NR^{19}-. R^{14} is selected from the group consisting of hydrogen, halogen, alkyl, alkoxyalkyl, alkylthioalkyl, alkenyl, alkynyl, hydroxy, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, cycloalkenyl, amino, cyano, aryl, arylalkyl, heterocyclic, and heterocyclic(alkyl),

R^{16}, R^{17}, and R^{19} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano; and

R^{21} and R^{22} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano;

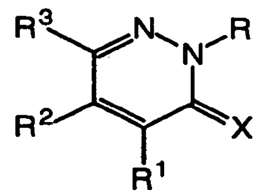
or their pharmaceutically acceptable salts, esters, or prodrugs thereof.

Detailed Description of the Invention

All patents, patent applications, and literature references cited in the specification are hereby incorporated by reference in their entirety. In the case of inconsistencies, the present disclosure, including definitions, will prevail.

The present invention discloses pyridazinone compounds which are cyclooxygenase (COX) inhibitors and are selective inhibitors of cyclooxygenase-2 (COX-2). COX-2 is the inducible isoform associated with inflammation, as opposed to the constitutive isoform, cyclooxygenase-1 (COX-1) which is an important "housekeeping" enzyme in many tissues, including the gastrointestinal (GI) tract and the kidneys.

In one embodiment, the compounds of the present invention have the formula **I**:



I

where

X is selected from the group consisting of O, S, NR^4, $N\text{-}OR^a$, and $N\text{-}NR^bR^c$, wherein R^4 is selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, heterocyclic, heterocyclic alkyl, and arylalkyl; and R^a, R^b, and R^c are independently selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, aryl, and arylalkyl;

R is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkylcarbonylalkyl, alkylsulfonylalkyl, alkylsulfonylarylalkyl, alkoxy, alkoxyalkyl, carboxy, carboxyalkyl, cyanoalkyl, haloalkyl, haloalkenyl, haloalkynyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, arylhaloalkyl, arylhydroxyalkyl, aryloxy, aryloxyhydroxyalkyl, aryloxyhaloalkyl, arylcarbonylalkyl, halolkoxyhydroxyalkyl, heterocyclic, heterocyclic alkyl, heterocyclic alkoxy, heterocyclic oxy, $-C(O)R^5$, $-(CH_2)_nC(O)R^5$, $-R^6\text{-}R^7$, $-(CH_2)_nCH(OH)R^5$, $-(CH_2)_nCH(OR^d)R^5$, $-(CH_2)_nC(NOR^d)R^5$, $-(CH_2)_nC(NR^d)R^5$, $-(CH_2)_nCH(NOR^d)R^5$, $-(CH_2)_nCH(NR^dR^e)R^5$, $-(CH_2)_nC{\equiv}C\text{-}R^7$, $-(CH_2)_n[CH(CX'_3)]_m\text{-}(CH_2)_n\text{-}CX'_3$, $-(CH_2)_n(C\,X'_2)_m\text{-}(CH_2)_n$

$-CX'_3$, $-(CH_2)_n[CH(CX'_3)]_m-(CH_2)_n-R^8$, $-(CH_2)_n(CX'_2)_m-(CH_2)_n R^8$, $-(CH_2)_n(CHX')_m-(CH_2)_n-CX'_3$, $-(CH_2)_n(CHX')_m-(CH_2)_n-R^8$, and $-(CH_2)_n-R^{20}$,

wherein R^5 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, haloalkenyl, haloalkynyl, heterocyclic, and heterocyclic alkyl;

wherein R^6 is alkylene or alkenylene, or halo-substituted alkylene halo-substituted alkenylene;

R^7 and R^8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclic, and heterocyclic alkyl;

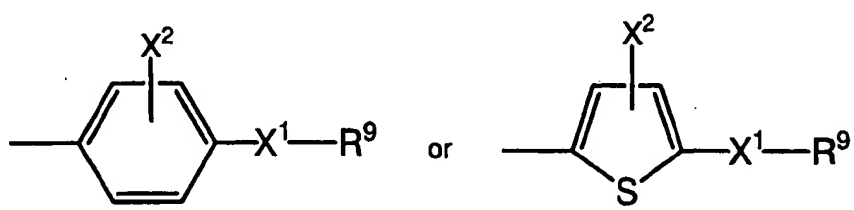
R^{20} is selected from the group consisting of alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkenyl, aryl, heterocyclic, and heterocyclic alkyl;

R^d and R^e are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclic, and heterocyclic alkyl;

X' is halogen;

n is from 0 to about 10, and m is 0 to about 5;

at least one of R^1, R^2 and R^3 is



where X^1 is selected from the group consisting of $-SO_2-$, $-SO(NR^{10})-$, $-SO-$, $-SeO_2-$, $PO(OR^{11})-$, and $-PO(NR^{12}R^{13})-$,

R^9 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, amino, $-NHNH_2$, $-N=CH(NR^{10}R^{11})$, dialkylamino, alkoxy, thiol, alkylthiol, protecting groups, and protecting groups attached to X^1 by an alkylene;

X^2 is selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, and alkynyl;

R^{10}, R^{11}, R^{12}, and R^{13} are independently selected from the group consisting of hydrogen, alkyl, and cycloalkyl, or R^{12} and R^{13} can be taken together, with the nitrogen to which they are attached, to form a heterocyclic ring having from 3 to 6 atoms.

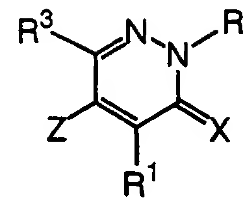
The remaining two of the groups of R^1, R^2, and R^3, are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, halogen, alkyl, alkenyl, alkynyl, alkylamino, alkenyloxy, alkylthio, alkylthioalkoxy, alkoxy, alkoxyalkyl, alkoxyalkylamino, alkoxyalkoxy, amido, amidoalkyl, haloalkyl, halolkenyloxy, haloalkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkenylalkoxy, cycloalkylalkoxy, cycloalkylalkylamino, cycloalkylamino, cycloalkyloxy, cycloalkylidenealkyl, amino, aminocarbonyl, aminoalkoxy, aminocarbonylalkyl, alkylaminoaryloxy, dialkylamino, dialkylaminoaryloxy, arylamino, arylalkylamino, diarylamino, aryl, arylalkyl, arylalkylthio, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, heterocyclic, heterocyclic alkyl, heterocyclic alkylamino, heterocyclic alkoxy, heterocyclic amino, heterocyclic oxy, heterocyclic thio, hydroxy, hydroxyalkyl, hydroxyalkylamino, hydroxyalkylthio, hydroxyalkoxy, mercaptoalkoxy, oxoalkoxy, cyano, nitro, and -Y-R^{14}, wherein Y is selected from the group consisting of -O-, -S-, -C(R^{16}) (R^{17})-, -C(O)N$R^{21}R^{22}$-, -C(O)-, -C(O)O-, -NH-, -NC(O)-, -N=C $R^{21}R^{22}$, N- $R^{21}R^{22}$, and -NR^{19}-. R^{14} is selected from the group consisting of hydrogen, halogen, alkyl, alkoxyalkyl, alkylthioalkyl, alkenyl, alkynyl, hydroxy, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, cycloalkenyl, amino, cyano, aryl, arylalkyl, heterocyclic, and heterocyclic(alkyl),

R^{16}, R^{17}, and R^{19} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano; and

R^{21} and R^{22} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano;

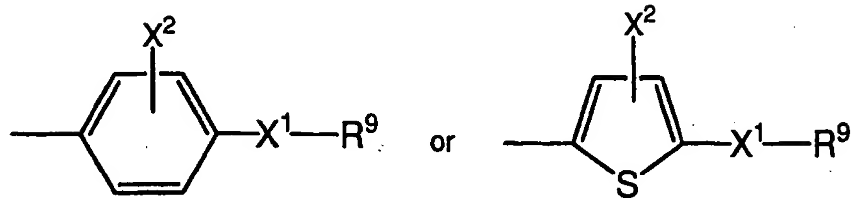
or a pharmaceutically acceptable salt, ester, or prodrug thereof.

In another embodiment, compounds of the present invention have the formula **II**:



II

wherein Z is a group having the formula:



where X^1 is selected from the group consisting of $-SO_2-$, $-SO-$, $-SeO_2-$,$SO(NR^{10})-$, and R^9 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, amino, $-NHNH_2$, dialkylamino, alkoxy, thiol, alkylthiol, protecting groups, and protecting groups attached to X' by an alkylene;

R^{10} is selected from the group consisting of hydrogen, alkyl, and cycloalkyl;

X^2 is selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, and alkynyl;

R is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkylcarbonylalkyl, alkylsulfonylalkyl, alkylsulfonylarylalkyl, alkoxy, alkoxyalkyl, carboxy, carboxyalkyl, cyanoalkyl, haloalkyl, haloalkenyl, haloalkynyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, arylhaloalkyl, arylhydroxyalkyl, aryloxy, aryloxyhydroxyalkyl, aryloxyhaloalkyl, arylcarbonylalkyl, haloalkoxyhydroxyalkyl, heterocyclic, heterocyclic alkyl, heterocyclic alkoxy, heterocyclic oxy, $-C(O)R^5$, $-(CH_2)_nC(O)R^5$, $-R^6-R^7$, $-(CH_2)_nCH(OH)R^5$, $-(CH_2)_nCH(OR^d)R^5$, $-(CH_2)_nC(NOR^d)R^5$, $-(CH_2)_nC(NR^d)R^5$, $-(CH_2)_nCH(NOR^d)R^5$, $-(CH_2)_nCH(NR^dR^e)R^5$, $-(CH_2)_nC{\equiv}C-R^7$, $-(CH_2)_n[CH(CX'_3)]_m-(CH_2)_n-CX'_3$, $-(CH_2)_n(C X'_2)_m-(CH_2)_n -CX'_3$, $-(CH_2)_n[CH(CX'_3)]_m-(CH_2)_n -R^8$, $-(CH_2)_n(C X'_2)_m-(CH_2)_n R^8$, $-(CH_2)_n(CHX')_m-(CH_2)_n - CX'_3$, $-(CH_2)_n(CHX')_m-(CH_2)_n -R^8$, and $-(CH_2)_n-R^{20}$,

wherein R^5 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, haloalkenyl, haloalkynyl, heterocyclic, and heterocyclic alkyl;

wherein R^6 is alkylene or alkenylene, or halo-substituted alkylene halo-substituted alkenylene;

R^7 and R^8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclic, and heterocyclic alkyl;

R^{20} is selected from the group consisting of alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkenyl, aryl, heterocyclic, and heterocyclic alkyl;

R^d and R^e are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclic, and heterocyclic alkyl;

X' is halogen;
n is from 0 to about 10, and m is 0 to about 5;

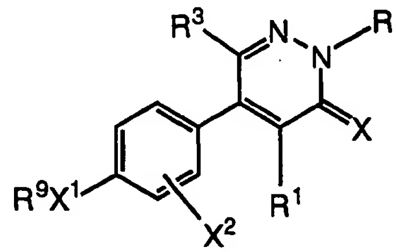
R^1, and R^3 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, halogen, alkyl, alkenyl, alkynyl, alkylamino, alkenyloxy, alkylthio, alkylthioalkoxy, alkoxy, alkoxyalkyl, alkoxyalkylamino, alkoxyalkoxy, amido, amidoalkyl, haloalkyl, halolkenyloxy, haloalkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkenylalkoxy, cycloalkylalkoxy, cycloalkylalkylamino, cycloalkylamino, cycloalkyloxy, amino, aminocarbonyl, aminoalkoxy, aminocarbonylalkyl, alkylaminoaryloxy, dialkylamino, dialkylaminoaryloxy, arylamino, arylalkylamino, diarylamino, aryl, arylalkyl, arylalkylthio, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, heterocyclic, heterocyclic alkyl, heterocyclic(alkyl) amino, heterocyclic alkoxy, heterocyclic amino, heterocyclic oxy, heterocyclic thio, hydroxy, hydroxyalkyl, hydroxyalkylamino, hydroxyalkoxy, mercaptoalkoxy, oxoalkoxy, cyano, nitro, and -Y-R^{14}, wherein Y is selected from the group consisting of -O-, -S-, -C(R^{16})(R^{17})-, -C(O)N$R^{21}R^{22}$-, -C(O)-, -C(O)O-, -NH-, -NC(O)-, -N=C $R^{21}R^{22}$, N-$R^{21}R^{22}$, and -NR^{19}-. R^{14} is selected from the group consisting of hydrogen, halogen, alkyl, alkoxyalkyl, alkylthioalkyl, alkenyl, alkynyl, hydroxy, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, cycloalkenyl, amino, cyano, aryl, arylalkyl, heterocyclic, and heterocyclic(alkyl),

R^{16}, R^{17}, and R^{19} are independently selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano; and

R^{21} and R^{22} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

In yet another embodiment, compounds of the present invention have the formula **III**:



III

wherein X, X^1, X^2, R, R^1, R^3, and R^9 are as defined in Formula **I**; or a pharmaceutically acceptable salt, ester, or prodrug thereof.

In a preferred embodiment, compounds of the present invention have the formula **III**, wherein X^1 is selected from the group consisting of $-SO_2-$, $-SO-$, $-SeO_2-$, and $-SO(NR^{10})-$, and R^9 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, amino, alkylamino, or dialkylamino;

X^2 is selected from the group consisting of hydrogen and halogen;

X is selected from the group consisting of O, S, NR^4, $N-OR^a$, and $N-NR^bR^c$, wherein R^4 is selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, heterocyclic, heterocyclic alkyl, and arylalkyl; and R^a, R^b, and R^c are independently selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, aryl, and arylalkyl;

R is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkylcarbonylalkyl, alkylsulfonylalkyl, alkylsulfonylarylalkyl, carboxyalkyl,

cyanoalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkenyl, arylalkynyl, heterocyclic, heterocyclic alkyl, arylalkyl, $-(CH_2)_nC(O)R^5$, $-(CH_2)_nC{\equiv}C-R^7$, $-(CH_2)_n[CH(CX'_3)]_m(CH_2)_n-R^8$, and $-(CH_2)n-R^{20}$;

wherein R^5 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, heterocyclic, and heterocyclic alkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, heterocyclic, and heterocyclic alkyl,

R^{20} is selected from the group consisting of alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkenyl, aryl, heterocyclic, and heterocyclic alkyl;

X' is halogen;

n is from 0 to about 10, m is from 0 to about 5;

$R^1$and R^3 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, halogen, alkyl, alkenyl, alkynyl, alkoxy, alkenyloxy, alkoxyalkyl, amido, amidoalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, amino, aminocarbonyl, aminocarbonylalkyl, alkylamino, dialkylamino, arylamino, arylalkylamino, diarylamino, aryl, aryloxy, heterocyclic, heterocyclic alkyl, cyano, nitro, and $-Y-R^{14}$, wherein Y is selected from the group consisting of, -O-, -S-, $-C(R^{16})(R^{17})-$, $-C(O)NR^{21}R^{22}-$, -C(O)-, -C(O)O-, -NH-, -NC(O)-, $-N{=}C R^{21}R^{22}$, $N- R^{21}R^{22}$, and $-NR^{19}-$. R^{14} is selected from the group consisting of hydrogen, halogen, alkyl, alkoxyalkyl, alkylthioalkyl, alkenyl, alkynyl, hydroxy, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, cycloalkenyl, amino, cyano, aryl, arylalkyl, heterocyclic, and heterocyclic(alkyl),

R^{16}, R^{17}, and R^{19} are independently selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano; and

R^{21} and R^{22} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

In another preferred embodiment, compounds of the present invention have the formula **III**, wherein X^1 is selected from the group consisting of $-SO_2-$, -SO-, $-SeO_2-$, and $-SO(NR^{10})-$, and R^9 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, amino, alkylamino, or dialkylamino;

X^2 is selected from the group consisting of hydrogen and halogen;

X is selected from the group consisting of O, S, NR^4, $N\text{-}OR^a$, and $N\text{-}NR^bR^c$, wherein R^4 is selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, alkylcycloalkenyl, aryl, heterocyclic, and arylalkyl; and R^a, R^b, and R^c.are independently selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, aryl, and arylalkyl;

R is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkylcarbonylalkyl, alkylsulfonylalkyl, alkylsulfonylarylalkyl, carboxyalkyl, cyanoalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkenyl, arylalkynyl, heterocyclic, heterocyclic alkyl, arylalkyl, $-(CH_2)_nC(O)R^5$, and $-(CH_2)n\text{-}R^{20}$;

wherein R^5 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, heterocyclic, and heterocyclic alkyl;

R^{20} is selected from the group consisting of alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkenyl, aryl, heterocyclic, and heterocyclic alkyl;

n is from 0 to about 10;

$R^1$and R^3 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, halogen, alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, alkylthioalkyl, aryloxyalkyl, arylthioalkyl, amido, amidoalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, amino, aminocarbonyl, aminocarbonylalkyl, alkylamino, alkylaminoalkyl, dialkylamino, arylamino, arylalkylamino, diarylamino, aryl, heterocyclic, heterocyclic(alkyl), cyano, nitro, and $-Y-R^{14}$, wherein Y is selected from the group consisting of, -O-, -S-, $-C(R^{16})(R^{17})-$, $-C(O)NR^{21}R^{22}-$, -C(O)-, -C(O)O-, -NH-, -NC(O)-, and $-NR^{19}-$. R^{14} is selected from the group consisting of hydrogen, halogen, alkyl, alkoxyalkyl, alkylthioalkyl, alkenyl, alkynyl, hydroxy, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, cycloalkenyl, amino, cyano, aryl, arylalkyl, heterocyclic, and heterocyclic(alkyl), and

R^{16}, R^{17}, and R^{19} are independently selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano;

R^{21} and R^{22} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

In another preferred embodiment, compounds of the present invention have the formula **III**, wherein X^1 is selected from the group consisting of $-SO_2-$, $-SO-$, $-SeO_2-$, and $-SO(NR^{10})-$, and R^9 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, amino, alkylamino, or dialkylamino;

X^2 is selected from the group consisting of hydrogen and halogen;

X is selected from the group consisting of O, S, NR^4, $N\text{-}OR^a$, and $N\text{-}NR^bR^c$, wherein R^4 is selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, alkylcycloalkenyl, aryl, heterocyclic, and arylalkyl; and R^a, R^b, and R^c.are independently selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, aryl, and arylalkyl;

R is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkylcarbonylalkyl, alkylsulfonylalkyl, alkylsulfonylarylalkyl, carboxyalkyl, cyanoalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkenyl, arylalkynyl, heterocyclic, heterocyclic alkyl, arylalkyl, and $-(CH_2)_nC(O)R^5$,;

wherein R^5 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, heterocyclic, and heterocyclic alkyl; and

n is from 0 to about 10;

$R^1$and R^3 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, halogen, alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, alkylthioalkyl, aryloxyalkyl, arylthioalkyl, amido, amidoalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, amino, aminocarbonyl, aminocarbonylalkyl, alkylamino, alkylaminoalkyl, dialkylamino, arylamino, arylalkylamino, diarylamino, aryl, heterocyclic, heterocyclic(alkyl), cyano, nitro, and $-Y-R^{14}$, wherein Y is selected from the group consisting of, -O-, -S-, $-C(R^{16})(R^{17})-$,

-C(O)NR^{21}R^{22}-, -C(O)-, -C(O)O-, -NH-, -NC(O)-, and -NR^{19}-. R^{14} is selected from the group consisting of hydrogen, halogen, alkyl, alkoxyalkyl, alkylthioalkyl, alkenyl, alkynyl, hydroxy, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, cycloalkenyl, amino, cyano, aryl, arylalkyl, heterocyclic, and heterocyclic(alkyl);

R^{15}, R^{16}, R^{17}, and R^{19} are independently selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl or cyano;

R^{21} and R^{22} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

In another preferred embodiment, compounds of the present invention have the formula **III**, wherein X^1 is selected from the group consisting of -SO_2-, -SO-, -SeO_2-, and -SO(NR^{10})-, and R^9 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, amino, alkylamino, or dialkylamino;

X^2 is selected from the group consisting of hydrogen and halogen;

X is selected from the group consisting of O, S, NR^4, N-OR^a, and N-NR^{b}R^c, wherein R^4 is selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, alkylcycloalkenyl, aryl, heterocyclic, and arylalkyl; and R^a, R^b, and R^c.are independently selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, aryl, and arylalkyl;

R is selected from alkyl, haloalkyl, aryl, heterocyclic, heterocyclic alkyl, and -(CH_2)n-R^{20} where is R^{20} is substituted and unsubstituted aryl wherein the substituted aryl compounds are substituted with halogen;

n is from 0 to about 10;

R^1 is selected from the group consisting of alkoxy, alkenyloxy, hydroxyalkoxy, aryloxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, and -Y-R^{14}, wherein Y is selected from the group consisting of, -O-, -S-, -C(R^{16}) (R^{17})-, -C(O)-, -C(O)O-, -NH-, -NC(O)-, and -NR^{19}-. R^{14} is selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkynyl, hydroxy, cycloalkyl, cycloalkenyl, amino, cyano, aryl, arylalkyl, heterocyclic, and heterocyclic alkyl,

R^3 is hydrogen;

R^{15}, R^{16}, R^{17}, and R^{19} are independently selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano; and

R^{21} and R^{22} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

In another preferred embodiment, compounds of the present invention have the formula **III**, wherein X^1 is selected from the group consisting of $-SO_2-$, -SO-, and $-SO(NR^{10})-$, and R^9 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, amino, alkylamino, or dialkylamino;

X^2 is selected from the group consisting of hydrogen and halogen;

X is selected from the group consisting of O, S, NR^4, $N-OR^a$, and $N-NR^bR^c$, wherein R^4 is selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, alkylcycloalkenyl, aryl, heterocyclic, and arylalkyl; and R^a, R^b, and R^c.are independently selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, aryl, and arylalkyl;

R is selected from alkyl, haloalkyl, aryl, heterocyclic, heterocyclic alkyl, and $-(CH_2)n-R^{20}$ where is R^{20} is substituted and unsubstituted aryl wherein the substituted aryl compounds are substituted with halogen;

n is from 0 to about 10;

R^1 is selected from the group consisting of alkoxy, alkenyloxy, hydroxyalkoxy, aryloxy, aryl, arylalkyl, heterocyclic, and heterocyclic alkyl; and

R^3 is hydrogen;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

In another preferred embodiment, compounds of the present invention have the formula **III**, wherein X^1 is $-SO_2-$ and and R^9 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, amino, alkylamino, or dialkylamino;

X^2 is selected from the group consisting of hydrogen and halogen;

X is selected from the group consisting of O, S, NR^4, N-OR^a, and N-NR^bR^c, wherein R^4 is selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, alkylcycloalkenyl, aryl, heterocyclic, and arylalkyl; and R^a, R^b, and R^c.are independently selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, aryl, and arylalkyl;

R is selected from haloalkyl, aryl, heterocyclic, heterocyclic alkyl, and -$(CH_2)n$-R^{20} where is R^{20} is substituted and unsubstituted aryl wherein the substituted aryl compounds are substituted with halogen;

n is from 0 to about 10;

R^1 is selected from the group consisting of unsubstituted aryl, and substituted aryl with one, two, or three substituents selected from the group consisting of fluorine and chlorine including, but not limited to, *p*-chlorophenyl, *p*-fluorophenyl, 3,4-dichlorophenyl, 3-chloro-4-fluoro-phenyl, and the like; and

R^3 is hydrogen;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

In another preferred embodiment, compounds of the present invention have the formula **III**, wherein X^1 is -SO_2-,and R^9 is selected from the group consisting of alkyl and amino;

X^2 is selected from the group consisting of hydrogen and halogen;

X is O;

R is selected from the group consisting of alkyl, alkenyl, alkynyl, haloalkyl, aryl, and arylalkyl;

R^1 is selected from the group consisting of alkoxy, aryl, alkenyloxy, hydroxyalkoxy, halalkoxy, arylalkyl, alkyl, and aryloxy; and

R^3 is hydrogen;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

In another preferred embodiment, compounds of the present invention have the formula **III**, wherein X^1 is -SO_2-, and R^9 is selected from the group consisting of alkyl and amino

X^2 is selected from hydrogen and fluorine;

R is selected from haloalkyl, aryl, and alkyl;

n is from 0 to about 10;

R^1 is selected from the group consisting of isobutyloxy, isopentyloxy, 1-(3-methyl-3-butenyl)oxy, 2-hydroxy-2-methyl-propyloxy, 3-hydroxy-3-methyl-butyloxy, neopentyloxy, isopentyl, aryloxy including 4-fluorophenoxy, unsubstituted aryl, and substitued aryl with one, two, or three substituents selected from the group consisting of fluorine and chlorine including, , 4-fluorophenyl, 4-chlorophenyl, 4-chloro-3-fluoro-phenyl, 3-chloro-4-fluoro-phenyl and the like; and

R^3 is hydrogen;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

In another preferred embodiment, compounds of the present invention have the formula **III**, wherein X^1 is selected from the group consisting of $-SO_2-$, and $-SO(NR^{10})-$, and R^9 is alkyl,

X^2 is selected from the group consisting of hydrogen and fluorine;

X is O;

R is selected from the group consisting of alkyl, alkenyl, alkynyl, haloalkyl, aryl, and arylalkyl;

R^1 is selected from the group consisting of alkoxy, aryl, alkenyloxy, hydroxyalkoxy, alkyl, and aryloxy; and

R^3 is hydrogen;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

In another preferred embodiment, compounds of the present invention have the formula **III**, wherein X^1 is $-SO_2-$, R^9 is amino;

X^2 is selected from the group consisting of hydrogen and fluorine;

X is O;

R is selected from the group consisting of alkyl, alkenyl, alkynyl, haloalkyl, aryl, and arylalkyl;

R^1 is selected from the group consisting of alkoxy, aryl, alkenyloxy, hydroxyalkoxy, alkyl, and aryloxy; and

R^3 is hydrogen;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

In another preferred embodiment, compounds of the present invention have the formula **III**, wherein X^1 is $-SO_2-$, and R^9 is methyl;

X^2 is selected from the group consisting of hydrogen;

X is O;

R is selected from the group consisting t-butyl, 3-chlorophenyl, 3,4-difluorophenyl, 4-fluorophenyl, 4-chloro-3-fluoro-phenyl, and CF_3CH_2-, ;

R^1 is selected from the group consisting of aryloxy including 4-fluorophenoxy, isobutyloxy, isopentyloxy, 1-(3-methyl-3-butenyl)oxy, 2-hydroxy-2-methyl-propyloxy, 3-hydroxy-3-methyl-butyloxy, neopentyloxy, isopentyl, 4-fluorophenyl, 4-chlorophenyl, 4-chloro-3-fluoro-phenyl, 3-chloro-4-fluoro-phenyl; and

R^3 is hydrogen;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

In another preferred embodiment, compounds of the present invention have the formula **III**, wherein X^1 is $-SO_2-$, and R^9 is amino;

X^2 is selected from the group consisting of hydrogen;

X is O;

R is selected from the group consisting t-butyl, 3-chlorophenyl, 3,4-difluorophenyl, 4-fluorophenyl, 4-chloro-3-fluoro-phenyl, 3-chloro-4-fluoro-phenyl and CF_3CH_2-, ;

R^1 is selected from the group consisting of aryloxy including 4-fluorophenoxy, isobutyloxy, isopentyloxy, 1-(3-methyl-3-butenyl)oxy, 2-hydroxy-2-methyl-propyloxy, 3-hydroxy-3-methyl-butyloxy, neopentyloxy, isopentyl, 4-fluorophenyl, 4-chlorophenyl, 4-chloro-3-fluoro-phenyl, 3-chloro-4-fluoro-phenyl; and

R^3 is hydrogen;

or a pharmaceutically acceptable salt, ester, or prodrug thereof

Definitions of Terms

As used throughout this specification and the appended claims, the following terms have the meanings specified.

The term "protecting groups includes "carboxy protecting group" and "N-protecyting groups" . "Carboxy protecting group" as used herein refers to a carboxylic acid protecting ester group employed to block or protect the carboxylic acid functionality while the reactions involving other functional sites of the compound are carried out. Carboxy protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis" pp. 152-186 (1981), which is hereby incorporated herein by reference. In addition, a carboxy protecting group can be used as a prodrug whereby the carboxy protecting group can be readily cleaved *in vivo* , for example by enzymatic hydrolysis, to release the biologically active parent. T. Higuchi and V. Stella provide a thorough discussion of the prodrug concept in "Pro-drugs as Novel Delivery Systems", Vol 14 of the A.C.S. Symposium Series, American Chemical Society (1975), which is hereby incorporated herein by reference. Such carboxy protecting groups are well known to those skilled in the art, having been extensively used in the protection of carboxyl groups in the penicillin and cephalosporin fields, as described in U.S. Pat. No. 3,840,556 and 3,719,667, the disclosures of which are hereby incorporated herein by reference. Examples of esters useful as prodrugs for compounds containing carboxyl groups can be found on pages 14-21 of "Bioreversible Carriers in Drug Design: Theory and Application", edited by E.B. Roche, Pergamon Press, New York (1987), which is hereby incorporated herein by reference. Representative carboxy protecting groups are C_1 to C_8 alkyl (e.g., methyl, ethyl or tertiary butyl and the like); haloalkyl; alkenyl; cycloalkyl and substituted derivatives thereof such as cyclohexyl, cylcopentyl and the like; cycloalkylalkyl and substituted derivatives thereof such as cyclohexylmethyl, cylcopentylmethyl and the like; arylalkyl, for example, phenethyl or benzyl and substituted derivatives thereof such as alkoxybenzyl or nitrobenzyl groups and the like; arylalkenyl, for example, phenylethenyl and the like; aryl and substituted derivatives thereof, for example, 5-indanyl and the like;

dialkylaminoalkyl (e.g., dimethylaminoethyl and the like); alkanoyloxyalkyl groups such as acetoxymethyl, butyryloxymethyl, valeryloxymethyl, isobutyryloxymethyl, isovaleryloxymethyl, 1-(propionyloxy)-1-ethyl, 1-(pivaloyloxyl)-1-ethyl, 1-methyl-1-(propionyloxy)-1-ethyl, pivaloyloxymethyl, propionyloxymethyl and the like; cycloalkanoyloxyalkyl groups such as cyclopropylcarbonyloxymethyl, cyclobutylcarbonyloxymethyl, cyclopentylcarbonyloxymethyl, cyclohexylcarbonyloxymethyl and the like; aroyloxyalkyl, such as benzoyloxymethyl, benzoyloxyethyl and the like; arylalkylcarbonyloxyalkyl, such as benzylcarbonyloxymethyl, 2-benzylcarbonyloxyethyl and the like; alkoxycarbonylalkyl, such as methoxycarbonylmethyl, cyclohexyloxycarbonylmethyl, 1-methoxycarbonyl-1-ethyl, and the like; alkoxycarbonyloxyalkyl, such as methoxycarbonyloxymethyl, t-butyloxycarbonyloxymethyl, 1-ethoxycarbonyloxy-1-ethyl,

1-cyclohexyloxycarbonyloxy-1-ethyl and the like; alkoxycarbonylaminoalkyl, such as t-butyloxycarbonylaminomethyl and the like; alkylaminocarbonylaminoalkyl, such as methylaminocarbonylaminomethyl and the like; alkanoylaminoalkyl, such as acetylaminomethyl and the like; heterocycliccarbonyloxyalkyl, such as 4-methylpiperazinylcarbonyloxymethyl and the like; dialkylaminocarbonylalkyl, such as dimethylaminocarbonylmethyl, diethylaminocarbonylmethyl and the like; (5-(loweralkyl)-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-t-butyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like; and (5-phenyl-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like.

The term "N-protecting group" or "N-protected" as used herein refers to those groups intended to protect the N-terminus of an amino acid or peptide or to protect an amino group against undersirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, "Protective Groups In Organic Synthesis," (John Wiley & Sons, New York (1981)), which is hereby incorporated by reference. N-protecting groups comprise acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl and the like; carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl,

3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl,

2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2,-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, phenylthiocarbonyl and the like; alkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. Preferred N-protecting groups are formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (t-Boc) and benzyloxycarbonyl (Cbz).

The term "alkanoyl" as used herein refers to an alkyl group as previously defined appended to the parent molecular moiety through a carbonyl (-C(O)-) group. Examples of alkanoyl include acetyl, propionyl and the like.

The term "alkanoylamino" as used herein refers to an alkanoyl group as previously defined appended to an amino group. Examples alkanoylamino include acetamido, propionylamido and the like.

The term "alkenyl" as used herein refers to a straight or branched chain hydrocarbon radical containing from 2 to 15 carbon atoms and also containing at least one carbon-carbon double bond. Alkenyl groups include, for example, vinyl (ethenyl), allyl (propenyl), butenyl, 1-methyl-2-buten-1-yl and the like.

The term "alkenylene" denotes a divalent group derived from a straight or branched chain hydrocarbon containing from 2 to 15 carbon atoms and also containing at least one carbon-carbon double bond. Examples of alkenylene include $-CH=CH-$, $-CH_2CH=CH-$, $-C(CH_3)=CH-$, $-CH_2CH=CHCH_2-$, and the like.

The term "alkenyloxy" as used herein refers to an alkenyl group, as previously defined, connected to the parent molecular moiety through an oxygen (-O-) linkage. Examples of alkenyloxy include isopropenoxy, butenyloxy and the like.

The term "alkoxy" as used herein refers to $R_{41}O-$ wherein R_{41} is a loweralkyl group, as defined herein. Examples of alkoxy include, but are not limited to, ethoxy, isobutyloxy, isopentyloxy, tert-butoxy, and the like.

The term "alkoxyalkylamino" as used herein refers to an alkoxy as defined herein appended to the parent molecular moiety through an alkylamino as defined herein. Examples of alkoxyalkylamino include, but are not limited to, ethoxymethylamino, isobutyloxyethylamino and the like

The term "alkoxyalkoxy" as used herein refers to $R_{80}O$-$R_{81}O$- wherein R_{80} is loweralkyl as defined above and R_{81} is alkylene. Representative examples of alkoxyalkoxy groups include methoxymethoxy, ethoxymethoxy, t-butoxymethoxy and the like.

The term "alkoxycarbonyl" as used herein refers to an alkoxyl group as previously defined appended to the parent molecular moiety through a carbonyl group. Examples of alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl and the like.

The term "alkoxycarbonylalkenyl" as used herein refers to an alkoxycarbonyl group as previously defined appended to the parent molecular moiety through an alkenylene. Examples of alkoxycarbonylalkenyl include methoxycarbonylethenylene, ethoxycarbonylpropenylene, and the like.

The term "alkoxyalkoxyalkyl" as used herein refers to an alkoxyalkoxy group as previously defined appended to an alkyl radical. Representative examples of alkoxyalkoxyalkyl groups include methoxyethoxyethyl, methoxymethoxymethyl, and the like.

The term "alkoxyalkoxyalkenyl" as used herein refers to an alkoxyalkoxy group as previously defined appended to an alkenyl radical. Representative examples of alkoxyalkoxyalkenyl groups include methoxyethoxyethenyl, methoxymethoxymethenyl, and the like.

The term "alkoxyalkyl" as used herein refers to an alkoxy group as previously defined appended to an alkyl radical as previously defined. Examples of alkoxyalkyl include, but are not limited to, methoxymethyl, methoxyethyl, isopropoxymethyl and the like.

The term "(alkoxycarbonyl)thioalkoxy" as used herein refers to an alkoxycarbonyl group as previously defined appended to a thioalkoxy radical. Examples of (alkoxycarbonyl)thioalkoxy include methoxycarbonylthiomethoxy, ethoxycarbonylthiomethoxy and the like.

The terms "alkyl" and "loweralkyl" as used herein refer to straight or branched chain alkyl radicals containing from 1 to 15 carbon atoms including, but

not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl, 1-methylbutyl, 2,2-dimethylbutyl, 2-methylpentyl, 2,2-dimethylpropyl, n-hexyl and the like.

The term "alkylamino" as used herein refers to $R_{51}NH$- wherein R_{51} is a loweralkyl group, for example, ethylamino, butylamino, and the like.

The term "alkylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended an alkylamino group.

The term "alkylaminocarbonyl" as used herein refers to an alkylamino group, as previously defined, appended to the parent molecular moiety through a carbonyl (-C(O)-) linkage. Examples of alkylaminocarbonyl include methylaminocarbonyl, ethylaminocarbonyl, isopropylaminocarbonyl and the like.

The term "alkylaminocarbonylalkenyl" as used herein refers to an alkenyl radical to which is appended an alkylaminocarbonyl group.

The term "alkylcarbonylalkyl" as used herein refers to R_{40}-C(O)- R_{41}- wherein R_{40} is an alkyl group and R_{41} is an alkylene group.

The term "alkylene" denotes a divalent group derived from a straight or branched chain saturated hydrocarbon having from 1 to 15 carbon atoms by the removal of two hydrogen atoms, for example $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$, $-CH_2CH_2CH_2-$, $-CH_2C(CH_3)_2CH_2-$ and the like.

The term "alkylsulfonyl" as used herein refers to an alkyl group as previously defined appended to the parent molecular moiety through a sulfonyl ($-S(O)_2-$) group. Examples of alkylsulfonyl include methylsulfonyl, ethylsulfonyl, isopropylsulfonyl and the like.

The term "alkylsulfonylalkyl" as used herein refers to an alkyl group as previously defined appended to the parent molecular moiety through a sulfonylalkyl ($-S(O)_2-R-$) group. Examples of alkylsulfonylalkyl include methylsulfonylmethyl, ethylsulfonylmethyl, isopropylsulfonylethyl and the like.

The term "alkylsulfonylamino" as used herein refers to an alkyl group as previously defined appended to the parent molecular moiety through a sulfonylamino ($-S(O)_2-NH-$) group. Examples of alkylsulfonylamino include methylsulfonylamino, ethylsulfonylamino, isopropylsulfonylamino and the like.

The term "alkylsulfonylarylalkyl" as used herein refers to an alkyl group as previously defined appended to the parent molecular moiety through a sulfonylalkyl

($-S(O)_2-R_{45}R_{33}-$) group wherein R_{45} is aryl and R_{33} is alkylene. Examples of alkylsulfonylarylalkyl include methylsulfonylphenylmethyl ethylsulfonylphenylmethyl, isopropylsulfonylphenylethyl and the like.

The term "alkylthio" as used herein refers to $R_{53}S-$ wherein R_{53} is alkyl.

The term "alkylthioalkyl" as used herein refers to alkylthio as defined herein appended to the parent molecular moiety through an alkylene group.

The term "alkylthioalkoxy" as used herein refers to alkylthio as defined herein appended to the parent molecular moiety through an alkoxyl group as defined herein.

The term "alkynyl" as used herein refers to a straight or branched chain hydrocarbon radical containing from 2 to 15 carbon atoms and also containing at least one carbon-carbon triple bond. Examples of alkynyl include -C≡C-H, H-C≡C-CH_2-, H-C≡C-CH(CH_3)- and the like.

The term "amido" as used herein refers to R54-C(O)-NH- wherein R_{54} is an alkyl group.

The term "amidoalkyl" as used herein refers to R_{34}-C(O)-NHR_{35}- wherein R_{34} is alkyl and R_{35} is alkylene.

The term "amino" as used herein refers $-NH_2$.

The term "aminoalkoxy" as used herein refers to an amino group appended to the parent molecular moiety through an alkoxyl group as defined herein.

The term "aminocarbonyl" as used herein refers to H_2N-C(O)-.

The term "aminocarbonylalkyl " as used herein refers to an aminocarbonyl as described above appended to the parent molecular moiety through an alkylene.

The term "aminocarbonylalkenyl" as used herein refers to an alkenyl radical to which is appended an aminocarbonyl ($NH_2C(O)$-) group.

The term "aminocarbonylalkoxy" as used herein refers to H_2N-C(O)- appended to an alkoxy group as previously defined. Examples of aminocarbonylalkoxy include aminocarbonylmethoxy, aminocarbonylethoxy and the like.

The term "aroyloxyalkyl" as used herein refers to R_{32}-C(O)-O-R_{33}- wherein R_{32} is an aryl group and R_{33} is an alkylene group. Examples of aroyloxyalkyl include benzoyloxymethyl, benzoyloxyethyl and the like.

The term "aryl" as used herein refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl and the like. Aryl groups can be unsubstituted or substituted with one, two or three substituents independently selected from loweralkyl, halo, haloalkyl, haloalkoxy, hydroxy, oxo (=O), hydroxyalkyl, alkenyloxy, alkoxy, alkoxyalkoxy, alkoxycarbonyl, alkoxycarbonylalkenyl, (alkoxycarbonyl)thioalkoxy, thioalkoxy, alkylimino ($R^*N=$ wherein R^* is a loweralkyl group), amino, alkylamino, alkylsulfonyl, dialkylamino, aminocarbonyl, aminocarbonylalkoxy, alkanoylamino, aryl, arylalkyl, arylalkoxy, aryloxy, mercapto, cyano, nitro, carboxy, carboxaldehyde, carboxamide, cycloalkyl, carboxyalkenyl, carboxyalkoxy, alkylsulfonylamino, cyanoalkoxy, heterocyclic alkoxy, $-SO_3H$, hydroxyalkoxy, phenyl and tetrazolylalkoxy. In the case of halo, aryl may have up to five halo substituents. Examples of substituted aryl include 3-chlorophenyl, 3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 3,4-dichlorophenyl, 3-chloro-4-fluoro-phenyl, 4-methylsulfonylphenyl, pentaflurophenyl, and the like.

The term "arylalkenyl" as used herein refers to an alkenyl radical to which is appended an aryl group, for example, phenylethenyl and the like.

The term "arylalkynyl" as used herein refers to an alkynyl radical to which is appended an aryl group, for example, phenylethynyl and the like

The term "arylalkoxy" as used herein refers to $R_{42}O$- wherein R_{42} is an arylalkyl group, for example, benzyloxy, and the like.

The term "arylalkoxyalkyl" as used herein refers to a loweralkyl radical to which is appended an arylalkoxy group, for example, benzyloxymethyl and the like.

The term "arylalkyl" as used herein refers to an aryl group as previously defined, appended to a loweralkyl radical, for example, benzyl and the like.

The term "arylalkylamino" as used herein refers to an arylalkyl group as previously defined, appended to the parent molecular moiety through an amino group.

The term "arylalkylthio" as used herein refers to an arylalkyl group as previously defined, appended to the parent molecular moiety through an thiol group.

The term "arylamino" as used herein refers to $R_{45}NH_2$- wherein R_{45} is an aryl.

The term “arylcarbonylalkyl” as used herein refers to $R_{45}C(O)R_{33}$- wherein R_{45} is an aryl group and R_{33} is an alkylene group.

The term “arylhaloalkyl” as used herein refers to an aryl group as previously defined, appended to the parent molecular moiety through a haloalkyl as defined herein. Examples of arylhaloalkyl include, phenyl-2-fluoropropyl, and the like.

The term “arylhydroxyalkyl” as used herein refers to an aryl group as previously defined, appended to the parent molecular moiety through a hydroxyalkyl as defined herein. Examples of arylhydroxyalkyl include, phenyl-2-hydroxypropyl, and the like.

The term “aryloxy” as used herein refers to $R_{45}O$- wherein R_{45} is an aryl group, for example, phenoxy, and the like.

The term “aryloxyalkyl” refers to an aryloxy group as previously defined appended to an alkyl radical. Examples of aryloxyalkyl include phenoxymethyl, 2-phenoxyethyl and the like.

The term “aryloxyhaloalkyl" as used herein refers to an aryloxy group as previously defined, appended to the parent molecular moiety through a haloalkyl as defined herein. Examples of aryloxyhaloalkyl include, phenyloxy-2-fluoropropyl, and the like.

The term “aryloxyhydroxyalkyl” as used herein refers to an aryloxy group as previously defined, appended to the parent molecular moiety through a hydroxyalkyl as defined herein. Examples of aryloxyhydroxyalkyl include, phenyoxy-2-hydroxypropyl, and the like.

The term “carboxaldehyde” as used herein refers to a formaldehyde radical, -C(O)H.

The term “carboxamide" as used herein refers to -C(O)NH_2.

The term “carboxy” as used herein refers to a carboxylic acid radical, -C(O)OH.

The term “carboxyalkyl" as used herein refers to a carboxy group as previously defined appended to an alkyl radical as previously defined. Examples of carboxyalkyl include 2-carboxyethyl, 3-carboxy-1-propyl and the like.

The term "carboxyalkenyl" as used herein refers to a carboxy group as previously defined appended to an alkenyl radical as previously defined.

Examples of carboxyalkenyl include 2-carboxyethenyl, 3-carboxy-1-ethenyl and the like.

The term "carboxyalkoxy" as used herein refers to a carboxy group as previously defined appended to an alkoxy radical as previously defined. Examples of carboxyalkoxy include carboxymethoxy, carboxyethoxy and the like.

The term "cyano" as used herein refers a cyano (-CN) group.

The term "cyanoalky" as used herein refers to an alkyl radical as previously defined to which is appended a cyano (-CN) group. Examples of cyanoalkyl include 3-cyanopropyl, 4-cyanobutyl, and the like.

The term "cyanoalkoxy" as used herein refers to a cyano (-CN) group appended to the parent molecular moiety through an alkoxy radical. Examples of cyanoalkoxy include 3-cyanopropoxy, 4-cyanobutoxy and the like.

The term "cycloalkanoyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended a cycloalkanoyloxy group (i.e., R_{60}-C(O)-O- wherein R_{60} is a cycloalkyl group).

The term "cycloalkyl" as used herein refers to an aliphatic ring system having 3 to 10 carbon atoms and 1 to 3 rings including, but not limited to, cyclopropyl, cyclopentyl, cyclohexyl, and the like. Cycloalkyl groups can be unsubstituted or substituted with one, two or three substituents independently selected from hydroxy, halo, oxo (=O), alkylimino (R*N= wherein R* is a loweralkyl group), amino, alkylamino, dialkylamino, alkoxy, alkoxyalkoxy, alkoxycarbonyl, thioalkoxy, haloalkyl, mercapto, carboxy, carboxaldehyde, carboxamide, cycloalkyl, aryl, arylalkyl, $-SO_3H$, nitro, cyano and loweralkyl.

The term "cycloalkenyl" as used herein refers to an aliphatic ring system having 3 to 10 carbon atoms and 1 to 3 rings containing at least one double bond in the ring structure. Cycloalkenyl groups can be unsubstituted or substituted with one, two or three substituents independently selected hydroxy, halo, oxo (=O), alkylimino (R*N= wherein R* is a loweralkyl group), amino, alkylamino, dialkylamino, alkoxy, alkoxyalkoxy, alkoxycarbonyl, thioalkoxy, haloalkyl, mercapto, carboxy, carboxaldehyde, carboxamide, cycloalkyl, aryl, arylalkyl , $-SO_3H$, nitro, cyano and loweralkyl.

The term "cycloalkylalkyl" as used herein refers to a cycloalkyl group appended to a loweralkyl radical, including but not limited to cyclohexylmethyl.

The term "cycloalkylalkoxy" as used herein refers to a cycloalkyl group appended to an alkoxyl group as defined herein, including but not limited to cyclohexylmethyoxy.

The term "cycloalkylamino" as used herein refers to a cycloalkyl group appended to the parent molecular moiety through an amino group as defined herein, including but not limited to cyclohexylamino and the like.

The term "cycloalkylalkylamino" as used herein refers to a cycloalkyl group appended to the parent molecular moiety through an alkylamino group as defined herein, including but not limited to cyclohexylmethylamino and the like.

The term "cycloalkylidenealkyl" as used herein refers to a cycloalkyl group appended to the parent molecular moiety through a double bond which connects to an alkylene ($=(CH_2)_n-$). Examples include cyclopropylideneethyl, cyclobutylidenepropyl and the like.

The term "cycloalkyloxy" as used herein refers to a cycloalkyl group appended to the parent molecular moiety through an oxygen atom, including but not limited to cyclohexyloxy and the like.

The term "cycloalkenylalkyl" as used herein refers to a cycloalkenyl group appended to a loweralkyl radical, including but not limited to cyclohexenylmethyl.

The term "cycloalkenylalkoxy" as used herein refers to a cycloalkenyl group appended to a alkoxyl group as defined herein, including but not limited to cyclohexenylmethyoxy and the like.

The term "dialkylamino" as used herein refers to $R_{56}R_{57}N-$ wherein R_{56} and R_{57} are independently selected from loweralkyl, for example diethylamino, methyl propylamino, and the like.

The term "dialkylaminoaryloxy" as used herein refers a dialkylamino as defined herein appended to the parent molecular moiety through an aryloxy as defined herein.

The term "diarylamino" as used herein refers to $(R_{45})(R_{46})N-$ wherein R_{45} and R_{46} are independently aryl, for example diphenylamino and the like.

The term "dialkylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended a dialkylamino group.

The term "dialkylaminocarbonyl" as used herein refers to a dialkylamino group, as previously defined, appended to the parent molecular moiety through a

carbonyl (-C(O)-) linkage. Examples of dialkylaminocarbonyl include dimethylaminocarbonyl, diethylaminocarbonyl and the like.

The term "dialkylaminocarbonylalkenyl" as used herein refers to an alkenyl radical to which is appended a dialkylaminocarbonyl group.

The term "dialkylaminocarbonylalkyl" as used herein refers to R_{50}-C(O)-R_{51}- wherein R_{50} is a dialkylamino group and R_{51} is an alkylene group.

The term "halo" or "halogen" as used herein refers to I, Br, Cl or F.

The term "haloalkyl" as used herein refers to an alkyl radical, as defined above, which has at least one halogen substituent, for example, chloromethyl, fluoroethyl, trifluoromethyl or pentafluoroethyl, 2,3-difluoropentyl, and the like.

The term "haloalkenyl" as used herein refers to an alkenyl radical which has at least one halogen substituent, for example, chloromethenyl, fluoroethenyl, trifluoromethenyl or pentafluoroethenyl, 2,3-difluoropentenyl, and the like.

The term "haloalkenyloxy" as used herein refers to an haloalkenyl group as defined herein appended to the parent molecular moiety through an oxygen atom.

The term "haloalkynyl" as used herein refers to an alkynyl radical which has at least one halogen substituent, for example, chloromethynyl, fluoroethynyl, trifluoromethynyl or pentafluoroethynyl, 2,3-difluoropentynyl, and the like.

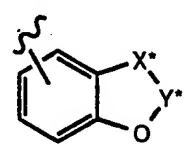
The term "haloalkoxy" as used herein refers to an alkoxy radical as defined above, bearing at least one halogen substituent, for example, 2-fluoroethoxy, 2,2,2-trifluoroethoxy, trifluoromethoxy, 2,2,3,3,3-pentafluoropropoxy and the like.

The term "haloalkoxyalkyl" as used herein refers to a loweralkyl radical to which is appended a haloalkoxy group.

The term "haloalkoxyhydroxyalkyl" as used herein refers to a haloalkoxy group as defined herein appended to the parent molecular moiety through a hydroxyalkyl, as defined herein.

The term "heterocyclic ring" or "heterocyclic" or "heterocycle" as used herein refers to any 3- or 4-membered ring containing a heteroatom selected from oxygen, nitrogen and sulfur; or a 5-, 6- or 7-membered ring containing one, two or three nitrogen atoms; one oxygen atom; one sulfur atom; one nitrogen and one sulfur atom; one nitrogen and one oxygen atom; two oxygen atoms in non-adjacent positions; one oxygen and one sulfur atom in non-adjacent positions; or two sulfur atoms in non-adjacent positions. Examples of heterocycles include, but are not

limited to, thiophene, pyrrole, and furan. The 5-membered ring has 0-2 double bonds and the 6- and 7-membered rings have 0-3 double bonds. The nitrogen heteroatoms can be optionally quaternized. The term "heterocyclic" also includes bicyclic groups in which any of the above heterocyclic rings is fused to a benzene ring or a cycloalkane ring or another heterocyclic ring (for example, indolyl, dihydroindolyl, quinolyl, isoquinolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, decahydroquinolyl, decahydroisoquinolyl, benzofuryl, dihydrobenzofuryl or benzothienyl and the like). Heterocyclics include: aziridinyl, azetidinyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, piperidinyl, homopiperidinyl, pyrazinyl, piperazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiomorpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, oxetanyl, furyl, tetrahydrofuranyl, thienyl, thiazolidinyl, isothiazolyl, triazolyl, tetrazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, pyrrolyl, pyrimidyl and benzothienyl.

Heterocyclics also include compounds of the formula  where X* is $-CH_2-$ or -O- and Y* is -C(O)- or $[-C(R'')_2-]_v$ where R" is hydrogen or C_1-C_4-alkyl and v is 1, 2 or 3 such as 1,3-benzodioxolyl, 1,4-benzodioxanyl and the like. Heterocyclics also include bicyclic rings such as quinuclidinyl and the like.

Heterocyclics can be unsubstituted or be substituted with one, two , or three substituents independently selected from hydroxy, halo, oxo (=O), alkylimino (R*N= wherein R* is a loweralkyl group), amino, alkylamino, dialkylamino, alkoxy, alkoxyalkoxy, alkoxycarbonyl, thioalkoxy, haloalkyl, mercapto, carboxy, carboxaldehyde, carboxamide, cycloalkyl, aryl, arylalkyl, $-SO_3H$, nitro, cyano and loweralkyl. In addition, nitrogen containing heterocycles can be N-protected.

The term "heterocyclic alkoxy" as used herein refers to a heterocyclic group as defined above appended to an alkoxy radical as defined above. Examples of heterocyclic(alkoxy) include 4-pyridylmethoxy, 2-pyridylmethoxy and the like.

The term "heterocyclic amino" as used herein refers to a heterocyclic group as defined above appended to an amino as defined above. Examples of heterocyclic amino include 4-pyridylamino, 2-pyridylamino and the like

The term "heterocyclic oxy" as used herein refers to a heterocyclic group as defined above appended to the parent molecular moiety through an oxygen. Examples of heterocyclic oxy include 4-pyridyloxy, 2-pyridyloxy and the like.

The term "heterocyclic alkyl" as used herein refers to a heterocyclic group as defined above appended to a loweralkyl radical as defined above.

The term "heterocyclic alkylamino" as used herein refers to a heterocyclic group as defined above appended to a alkylamino as defined above

The term "heterocyclic carbonyloxyalkyl" as used herein refers to R_{46}-C(O)-O-R_{47}- wherein R_{46} is a heterocyclic group and R_{47} is an alkylene group.

The term "heterocyclic thio" as used herein refers to a heterocyclic group as defined above appended to the parent molecular moiety through an thiol. Examples of heterocyclic thio include 4-pyridylthio, 2-pyridylthio and the like

The term "hydroxy" as used herein refers to -OH.

The term "hydroxyalkenyl" as used herein refers to an alkenyl radical to which is appended a hydroxy group. Examples of hydroxyalkenyl include 3-hydroxypropenyl, 3, 4-dihydroxybutenyl and the like

The term "hydroxyalkoxy" as used herein refers to an alkoxy radical as previously defined to which is appended a hydroxy (-OH) group. Examples of hydroxyalkoxy include 3-hydroxypropoxy, 4-hydroxybutoxy and the like.

The term "hydroxyalkyl" as used herein refers to a loweralkyl radical to which is appended a hydroxy group. Examples of hydroxyalkyl include 1-hydroxypropyl, 4-hydroxybutyl, 1,3-dihydroxyisopentyl, and the like.

The term "hydroxyalkylamino" as used herein refers to a hydroxyalkyl group appenmded to the parent molecular moiety through an amino. Examples of hydroxyalkylamino include 1-hydroxypropylamino, 4-hydroxybutylamino, 1,3-dihydroxyisopentylamino, and the like.

The term "hydroxyalkylthio" as used herein refers to a hydroxyalkyl group appenmded to the parent molecular moiety through an thiol. Examples of hydroxyalkylamino include 1-hydroxypropylthio, 4-hydroxybutylthio, 1,3-dihydroxyisopentylthio, and the like

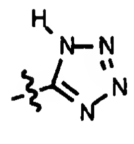
The term "mercapto" or "thiol" as used herein refers to -SH.

The term “nitro” as used herein refers to $-NO_2$.

The term oxoalkoxy refers to a carbonyl group attached to the parent molecular moiety through an alkoxy group.

The term "mercaptoalkoxy" or "thioalkoxy" as used herein refers to $R_{70}S$- wherein R_{70} is alkoxy. Examples of thioalkoxy include, but are not limited to, methylthio, ethylthio and the like.

The term "tetrazolyl" as used herein refers to a radical of the formula

 or a tautomer thereof.

The term "tetrazolylalkoxy" as used herein refers to a tetrazolyl radical as defined above appended to an alkoxy group as defined above. Examples of tetrazolylalkoxy include tetrazolylmethoxy, tetrazolylethoxy and the like.

The term "thioalkoxyalkoxy" as used herein refers to $R_{80}S$-$R_{81}O$- wherein R_{80} is loweralkyl as defined above and R_{81} is alkylene. Representative examples of alkoxyalkoxy groups include CH_3SCH_2O-, $EtSCH_2O$-, t-$BuSCH_2O$- and the like.

The term "thioalkoxyalkoxyalkyl" as used herein refers to a thioalkoxyalkoxy group appended to an alkyl radical. Representative examples of alkoxyalkoxyalkyl groups include $CH_3SCH_2CH_2OCH_2CH_2$-, $CH_3SCH_2OCH_2$-, and the like.

The compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. These salts include but are not limited to the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as loweralkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides,

aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid.

Basic addition salts can be prepared *in situ* during the final isolation and purification of the compounds of formula (I), or separately by reacting a carboxylic acid function with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia, or an organic primary, secondary or tertiary amine. Such pharmaceutically acceptable salts include, but are not limited to, cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, aluminum salts and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. Other representative organic amines useful for the formation of base addition salts include diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like.

The term "pharmaceutically acceptable ester" as used herein refers to esters which hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters includes formates, acetates, propionates, butyates, acrylates and ethylsuccinates.

The term "pharmaceutically acceptable prodrug" as used herein refers to those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "prodrug" refers to compounds that are rapidly transformed *in vivo* to provide the parent compound having the above formula, for

example by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

As used throughout this specification and the appended claims, the term metabolically cleavable group denotes a moiety which is readily cleaved *in vivo* from the compound bearing it, wherein said compound, after cleavage remains or becomes pharmacologically active. Metabolically cleavable groups form a class of groups reactive with the carboxyl group of the compounds of this invention are well known to practitioners of the art. They include, but are not limited to groups such as, for example, alkanoyl, such as acetyl, propionyl, butyryl, and the like; unsubstituted and substituted aroyl, such as benzoyl and substituted benzoyl; alkoxycarbonyl, such as ethoxycarbonyl; trialkylsilyl, such as trimethyl- and triethysilyl; monoesters formed with dicarboxylic acids, such as succinyl, and the like. Because of the ease with which the metabolically cleavable groups of the compounds of this invention are cleaved *in vivo*, the compounds bearing such groups act as pro-drugs of other prostaglandin biosynthesis inhibitors. The compounds bearing the metabolically cleavable groups have the advantage that they may exhibit improved bioavailability as a result of enhanced solubility and/or rate of absorption conferred upon the parent compound by virtue of the presence of the metabolically cleavable group.

Asymmetric centers may exist in the compounds of the present invention. The present invention contemplates the various stereoisomers and mixtures thereof. Individual stereoisomers of compounds of the present invention are made by synthesis from starting materials containing the chiral centers or by preparation of mixtures of enantiomeric products followed by separation as, for example, by conversion to a mixture of diastereomers followed by separation by recrystallization or chromatographic techniques, or by direct separation of the optical enantiomers on chiral chromatographic columns. Starting compounds of particular stereochemistry are either commercially available or are made by the methods detailed below and resolved by techniques well known in the organic chemical arts.

Preferred Embodiments

Compounds useful in practicing the present invention include, but are not limited to:

2-(2,2,2-Trifluoroethyl)-4-(4-chlorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(3-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3-Chlorophenyl)-4-(3-methyl-3-butenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(2,2,2-Trifluoroethyl)-4-(4-chloro-3-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-fluorophenyl)-4-(4-flurophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(3-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(*t*-Butyl)-4-(3-methylbutoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(*t*-Butyl)-4-(3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(2,2,2-Trifluoroethyl)-4-(2,2-dimethylpropoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(2,2,2-Trifluoroethyl)-4-(2-methylpropoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(3-methylbutoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(3-methylbutyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3-Chlorophenyl)-4-(3-methylbutoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3-Chlorophenyl)-4-(3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(2-methylpropoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3-Chlorophenyl)-4-(2-methylpropoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(3-methylbutoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(2-methylpropoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(2-methylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(2-methylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(4-fluorophenoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(4-fluorophenoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(2,2,2-Trifluoroethyl)-4-(2,2-dimethylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Chloro-3-fluorophenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(4-fluorophenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)- -4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]- 3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2,4-Bis(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-3(2H)-pyridazinone;

2-(4-fluorophenyl)-4-(4-flurophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone; and

2-(3,4-Difluorophenyl)-4-(2-hydroxy-2-methylpropoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(2-oxopropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(2-methoxy-imino-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

(R)-2-(3,4-Difluorophenyl)-4-(3-hydroxy-2-methylpropoxy)-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone;

(S)- 2-(3,4-Difluorophenyl)-4-(3-hydroxy-2-methylpropoxy)-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone;

(R)-2-(3,4-Difluorophenyl)-4-(3-hydroxy-2-methylpropoxy)-5-[4-(aminosulfonyl)-phenyl]-3(2H)-pyridazinone;

(S)- 2-(3,4-Difluorophenyl)-4-(3-hydroxy-2-methylpropoxy)-5-[4-(aminosulfonyl)-phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(3-oxo-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(3-oxo-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone; and

2,4-Bis(4-Flurophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

More preffered compounds of the present invention include, but are not limited to:

2-Phenyl-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-3(2H)-pyridazinone;
2-(2,2,2-Trifluoroethyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-3(2H)-pyridazinone;

2-(2,2,2-Trifluoroethyl)-4-(4-chlorophenyl)-5-(4-methylsulfonylphenyl)-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(2-methylpropoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone; and

2,4-Bis(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-3(2H)-pyridazinone;

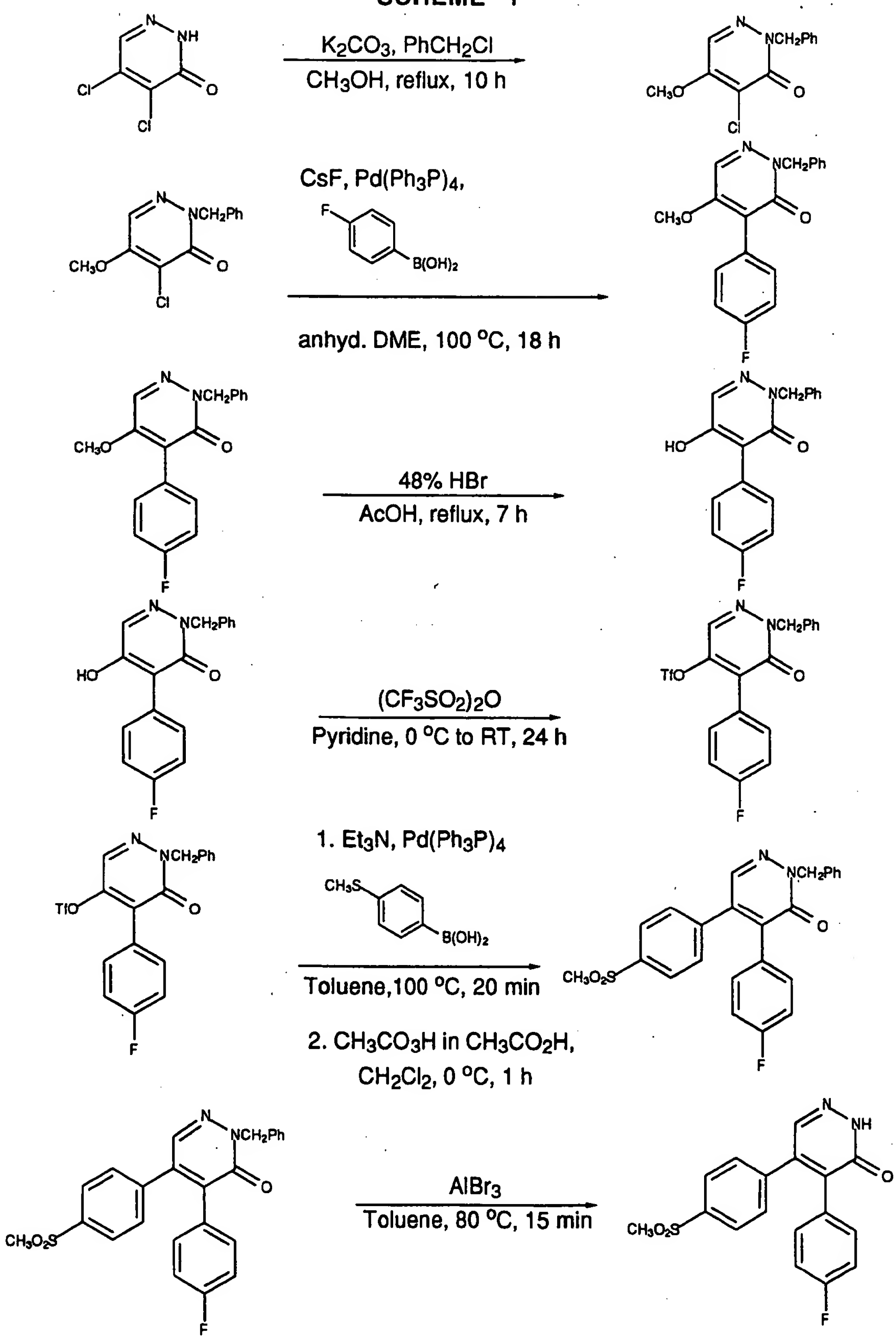
or a pharmaceutically acceptable salt, ester, or prodrug thereof.

Preparation of Compounds of the Invention

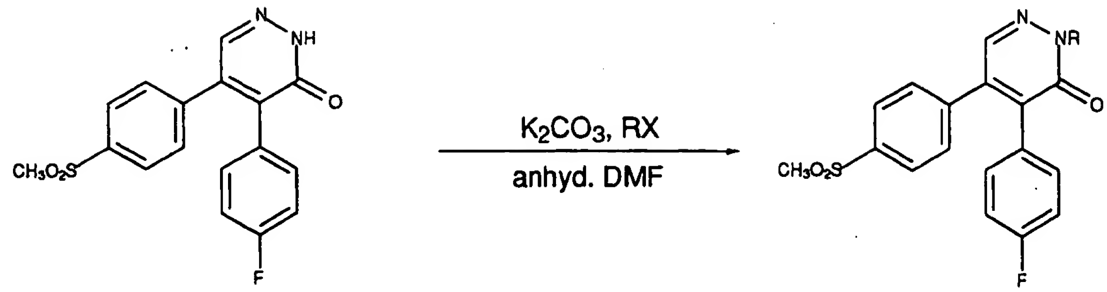
The compounds of the invention may be prepared by a variety of synthetic routes. Representative procedures are outlined in Schemes1-3, below.

A general route to the compounds of the invention having Formula **III**, where the aryl group at the 5-position on the pyridazinone ring is substituted with a sulfonyl group is described in Scheme 1, below. The dichloro-3(2H)-pyridazinone is reacted with benzyl chloride and potassium carbonate in methanol. The 2-benzyl-4-chloro-5-methoxy-3(2H)-pyridazinone is then treated with a boronic acid such as 4-fluorobenzeneboronic acid (shown) and a palladium catalyst. The methoxy group was hydrolyzed with 48% hydrobromic acid to furnish the 5-hydroxypyridazinone compound. The 5-hydroxypyridazinone product was treated with triflic anhydride followed by substitution on the pyridazinone ring using 4-methylthiobenzeneboronic acid. This furnished the methyl thioether compound which was reacted with peracetic acid in acetic acid and methylene chloride to provide the methyl sulfone. The benzyl group is removed using aluminum bromide or another suitable Lewis acid. The R group can be added via substitution using an appropriate alkylating agent and base.

SCHEME 1

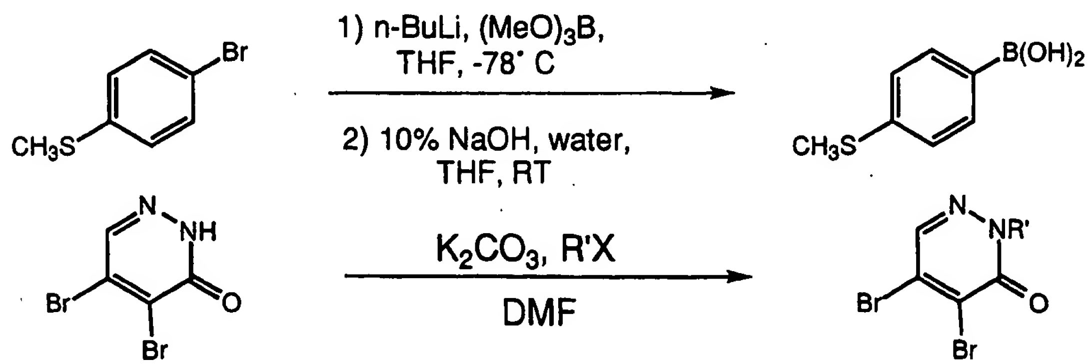


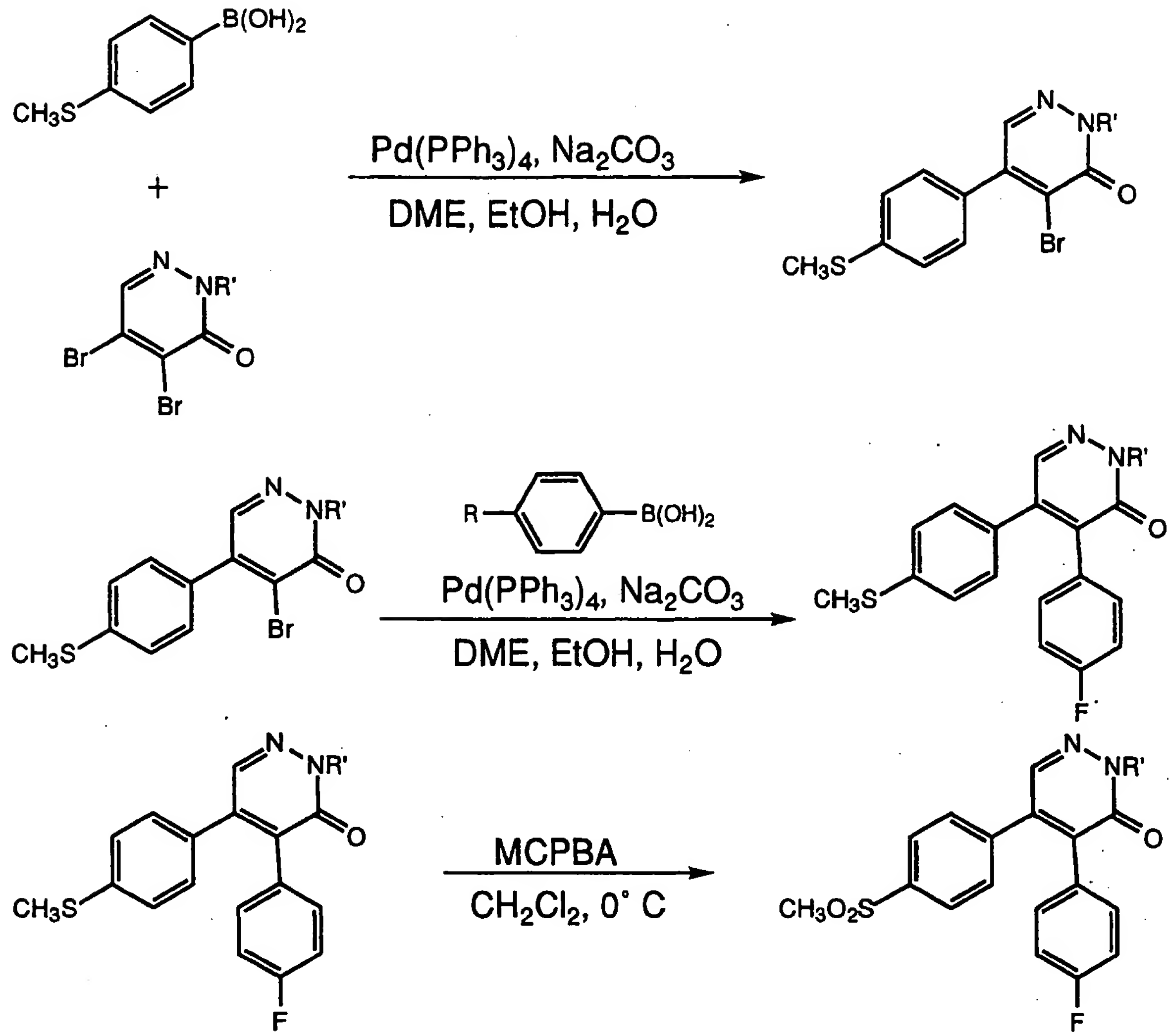
N
NH
Cl
Cl
O
K2CO3, PhCH2Cl
CH3OH, reflux, 10 h
NCH2Ph
CH3O
CsF, Pd(Ph3P)4,
F
B(OH)2
anhyd. DME, 100 °C, 18 h
48% HBr
AcOH, reflux, 7 h
HO
(CF3SO2)2O
Pyridine, 0 °C to RT, 24 h
TfO
1. Et3N, Pd(Ph3P)4
CH3S
Toluene,100 °C, 20 min
2. CH3CO3H in CH3CO2H,
CH2Cl2, 0 °C, 1 h
CH3O2S
AlBr3
Toluene, 80 °C, 15 min



Another route to the compounds of the invention having Formula **III** is described in Scheme 2, below. The 4-bromothioanisole or other suitable thioether is reacted with a trialkoxyborate, such as trimethoxyborate or triisopropylborate to convert it to 4-(Methylthio)benzeneboronic acid . The boronic acid is reacted with 2-benzyl-4,5-dibromo-3(2H)-pyridazinone using tetrakis(triphenylphosphine)-palladium (0) in dimethoxyethane. The product is then coupled with a second boronic acid such as 4-fluorobenzeneboronic acid (shown) and a palladium catalyst to provide the thioether. This furnished the methyl thioether compound which was reacted with meta-chloroperoxybenzoic acid (MCPBA) in methylene chloride to provide the methyl sulfone. The benzyl group is removed using aluminum bromide or another suitable Lewis acid. The R group can be added via substitution using an appropriate alkylating agent and base.

SCHEME 2

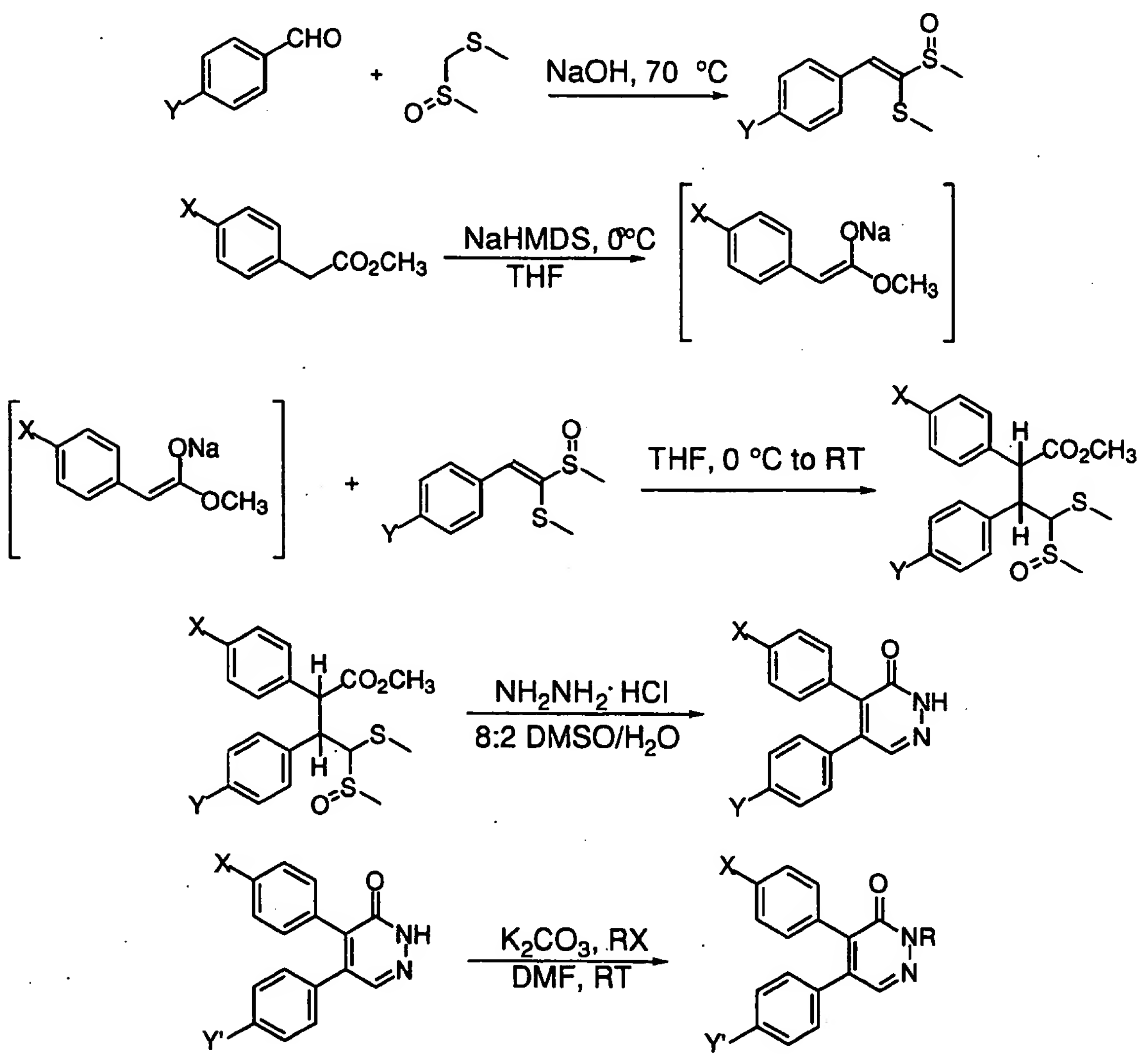




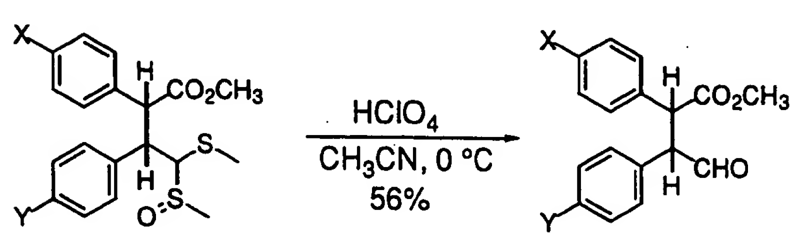
A third route to the compounds of the invention having Formula **III** is described in Scheme 3, below. (4-Thiomethylphenyl)dimethylthioketene acetal, mono-S-oxide was prepared by reaction of 4-thiomethylbenzaldehyde (Y is CH3S) with methyl(methylsulfinylmethyl)sulfide and sodium hydroxide. The thioketene acetal and methyl 4-fluorophenylacetate or suitable ester (X is fluorine) were treated with a strong base such as sodium hexamethyldisilazide in THF to provide the butyrate ester. The dithioacetal ketene was directly cyclized to the unsubstituted pyridazinone using hydrazine and a salt. The pyridazinone was oxidized with peroxyacetic acid to provide the sulfonyl pyridazone. In an alternate route, Scheme 3-A, the thioacetal ketene was treated with perchloric acid to provide an ester-aldehyde as a mixture of diastereomers. The oxidation products were treated with hydrazine and then oxidized with peroxyacetic acid to obtain the

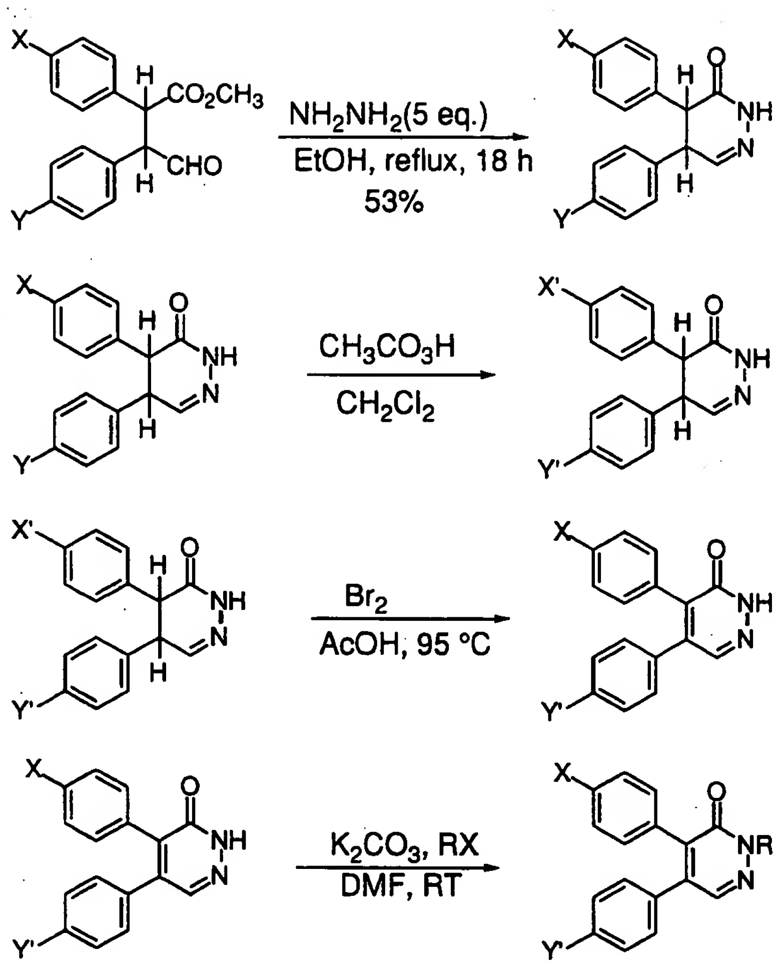
sulfonyl dihydropyridazinone. The dihydropyridazinone can be dehydrogenated to form the pyridazinone by treatment with reagents such as bromine in acetic acid. The R group may be added via substitution using an appropriate alkylating agent and base.

SCHEME 3



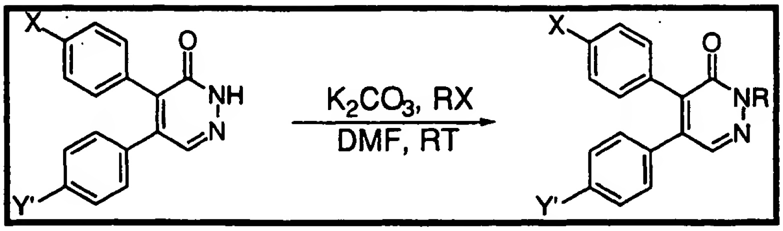
SCHEME 3A



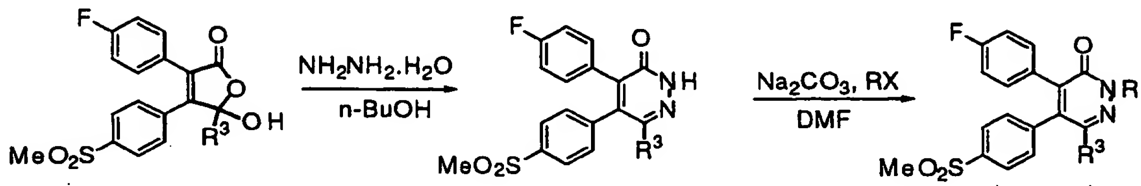


The preparation of the 5-hydroxy-2(5H)-furanones can be accomplished by the application of methodologies published in a variety of sources, including: J. Med. Chem., **1987**, *30*, 239-249 and WO 96/36623, hereby completely incorporated by reference, and are shown in Scheme 4.

SCHEME 4



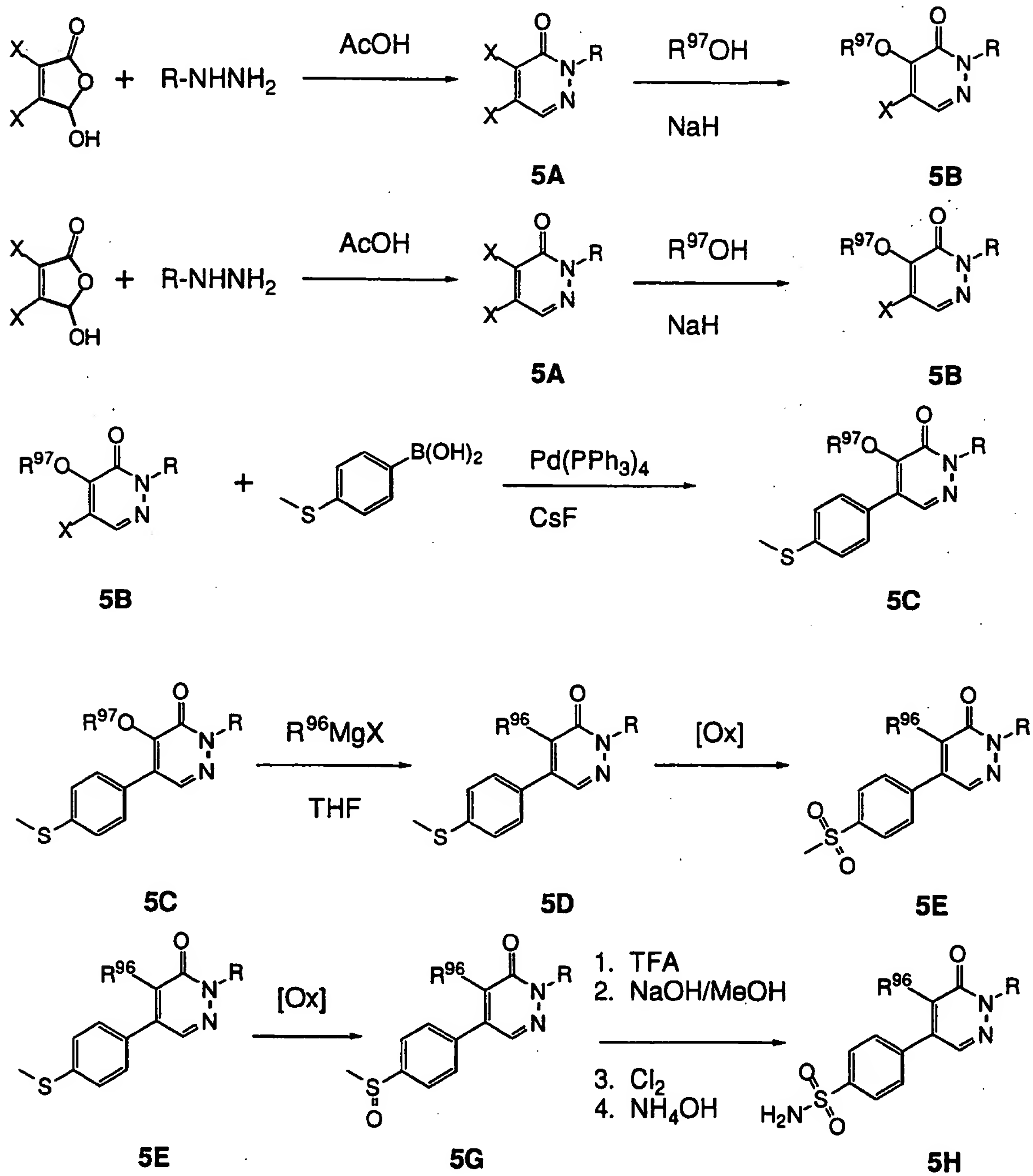
Method IV:

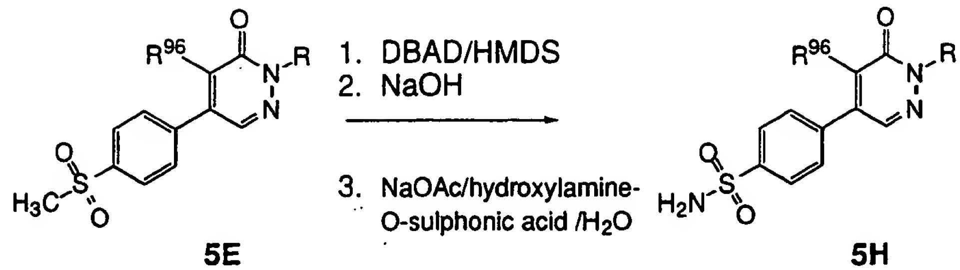


A general route to the compounds of the invention having Formula **III**, where the aryl group at the 5-position on the pyridazinone ring is substituted with a sulfonyl group ring is described in Scheme 5, below. A mucohalo acid, such as, for example, mucobromic or mucochloric acid, is reacted with an hydrazine having the desired R group to provide the dihalopyridazinone compound, **5A**. Treatment of the dihalo-compound with an alcohol in the presence of a base, such as, for example, sodium or potassium hydride, will provide an alkoxide, **5B**. (If the alkoxy group is to be removed at a later time then methanol is the preferred alcohol.) Reaction of the alkoxy-halide with a methylthiophenyl boronic will provide the alkoxy-pyridazinone **5C**. The alkoxy group can be converted to a hydrocarbyl group by treatment with a Grignard reagent to provide the thioether **5D**. The thioether can be oxidized with an oxidizing agent, such as, for example, peracetic acid, meta-chloroperoxybenzoic acid and the like, to form the sulfinyl compound **5G**, or the methylsulfone compound **5E**. Rearrangement and hydrolysis of the sulfinyl compound, **5G**, provides the thiophenol. The thiophenol is then oxidized, activated and aminated to convert it to the amino-sulfonyl compound **5H**. Alternatively, the methylsulfonyl compound, **5E**, can be converted to the amino-sulfonyl compound by **5H** by treatment of the methylsulfonyl compound with a diazodicarboxylate, such as, for example, DBAD, DIAD, DEAD and the like, and a disilazane anion, such as, for example, lithium HMDS and the like, followed by

treatment with sodium acetate and hydroxylamine-O-sulphonic acid in water provides the aminosulfonyl compound, **5H**.

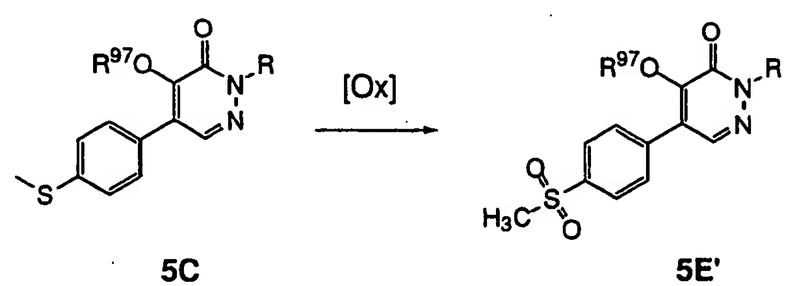
SCHEME 5

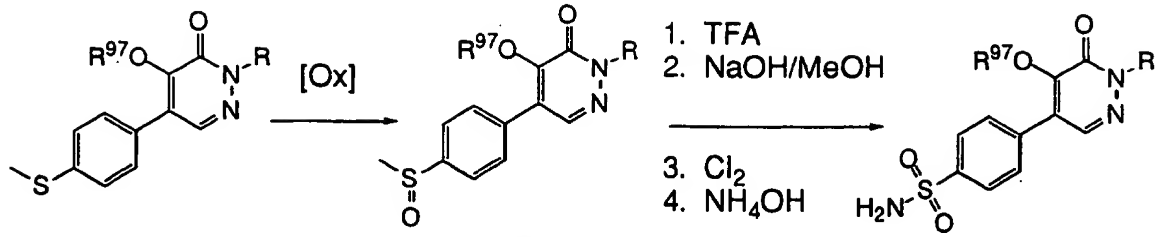




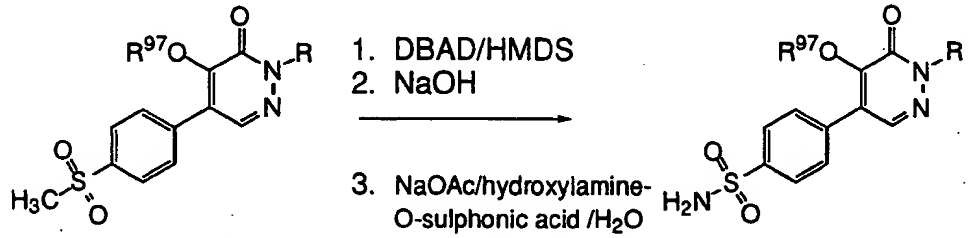
Alternatively, the alkoxy-pyridazinone **5C** can be oxidized, as shown in Scheme 5A. The first step is employing an oxidizing agent, such as, for example, peracetic acid, meta-chloroperoxybenzoic acid and the like, to form the sulfinyl compound **5G'**, or the methylsulfone compound **5E'**. Rearrangement and hydrolysis of the sulfinyl compound provides the thiophenol. The thiophenol is then oxidized, activated and aminated to convert it to the amino-sulfonyl compound **5H'**. Finally, the methylsulfonyl compound can be converted to the aminosulfonyl compound by **5H'** by treatment of the methylsulfonyl compound **5E'** with a diazodicarboxylate, such as, for example, DBAD, DIAD, DEAD and the like, and a disilazane anion, such as, for example, lithium HMDS and the like, followed by treatment with sodium acetate and hydroxylamine-O-sulphonic acid in water provides the aminosulfonyl compound, **5H'**.

SCHEME 5A





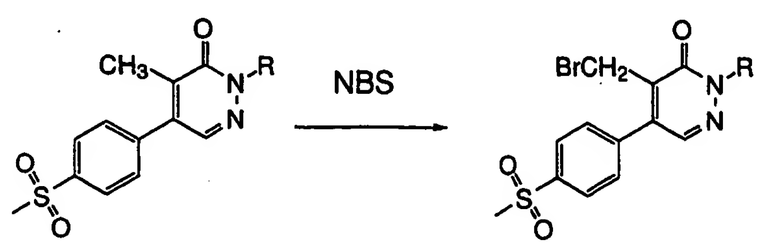
5C **5G'** **5H'**



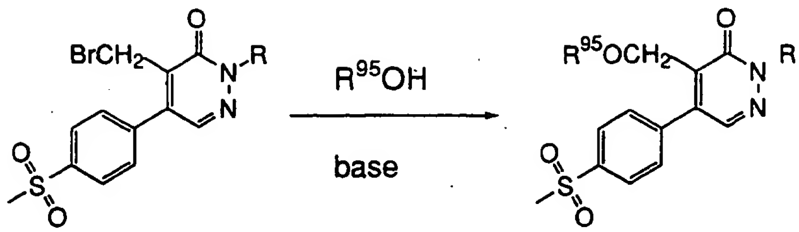
5E' **5H'**

Preparation of compounds of the invention having Formula **III**, where the group at the 4-position on the pyridazinone ring is a substituted alkyl or alkenyl group is described in Scheme 6A, below. The thioether **5E**, where R^{96} is alkyl, *e.g.*, methyl shown, is halogenated with a halogenating reagent, such as, for example, NBS and peroxide, to provide the bromo compound **6A**. The bromo compound can be reacted with an alcohol and a weak base, such as, for example, sodium or potassium carbonate to provide the 4-alkyl-ether, **6B**. The bromo compound can be reacted with a thio compound in the presence of a base, such as, for example, silver carbonate, to provide the 4-alkyl-thioether, **6C**. The bromo compound can be reacted with an amine and a weak base, such as, for example, sodium or potassium carbonate to provide the 4-alkyl amino-alkyl compound **6D**.

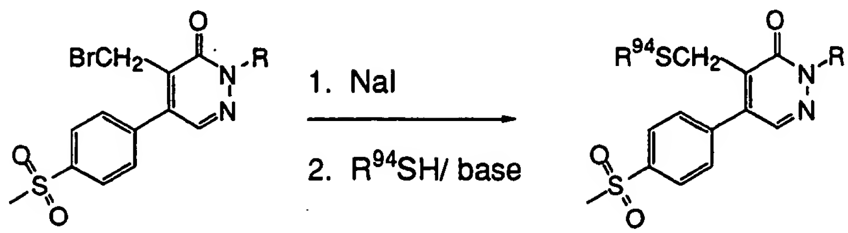
SCHEME 6



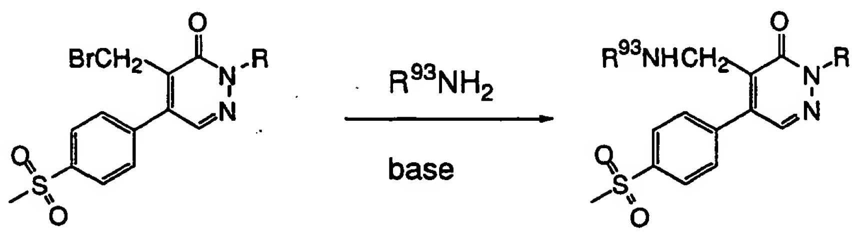
4E **5A**



5A **5B**



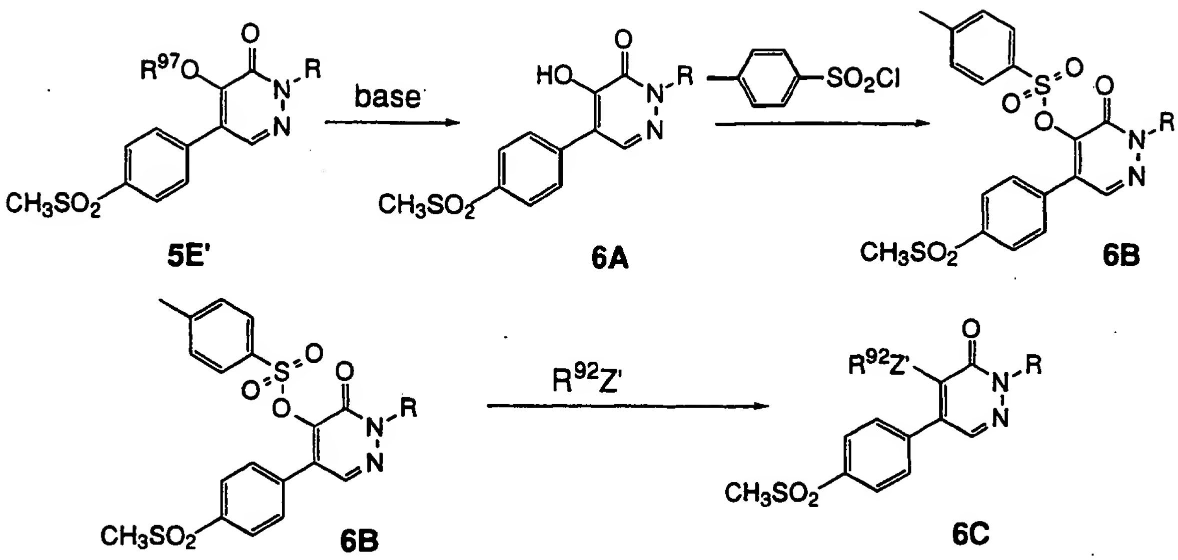
5A **5C**



5A **5D**

A general route to the compounds of the invention having Formula **III**, where the group at the 4-position on the pyridazinone ring can be readily substituted is illustrated in Scheme 6, above. The synthesis starts with the alkoxide, **5E'**, where R^{97} is methyl. The methoxy compound is treated with a base, such as, for example, sodium or potassium hydroxide, to provide the 4-hydroxy-pyradizinone, **6A**. The alcohol is treated with p-toluenesulfonyl chloride to provide the tosyloxy compound, **6B**. The tosyloxy compound can be readily substituted with a compound $R^{92}Z'$ that can undergo an S_N2 reaction. Examples of these compounds are compounds such as alcohols, thiols, amines or hydrocarbyl anions.

SCHEME 6A



As used throughout this specification and the appended claims, the following abbreviations have been used:

ACD for acid citrate dextrose, CAP for carrageenan induced air pouch prostaglandin, CIP for rat carrageenan pleural inflammation model, COX-2 for cyclooxygenase-2, CPE for carrageenan induced paw edema in rats, DBAD for di-t-butylazodicarboxylate, DEAD for diethyl azodicarboxylate, DIAD for disopropyl azodicarboxylate, DMAP for 4-(dimethylamino)pyridine, DME for 1,2-dimethoxyethane, DMF for N,N-dimethylformamide, DMSO for dimethyl sulfoxide, DMSO for dimethyl sulfoxide, EDTA for ethylenediaminetetraacetic acid, EIA for enzyme immunoassay, FAB for fast atom bombardment, GI for gastrointestinal, HMDS, lithium or Li HMDS for lithium 1,1,1,3,3,3-hexamethyldisilazide, HWPX for Human Whole Platelet Cyclooxygenase-1, MCPBA for meta-chloroperoxybenzoic acid, NSAIDs for non-steroidal anti-inflammatory drugs, PEG 400 for polyethyleneglycol, PGE_2 for prostaglandin E_2, PGHS for prostaglandin endoperoxide H synthase, RHUCX1 for recombinant human cyclooxygenase-1, RHUCX2 for recombinant human cyclooxygenase-2, r-hu Cox1 for recombinant human Cox-1, TEA for Triethylamine, TFA for Trifluoroacetic acid, and THF for Tetrahydrofuran and WISH for human amnionic whole cell cyclooxygenase-2. The following examples illustrate the process of the invention, without limitation.

Compounds of the present invention include, but are not intended to be limited to, the following Examples:

Example 1

4-(Methylthio)benzeneboronic acid

A stirred solution of 4-bromothioanisole (5.0 g, 0.0246 mol) in anhydrous tetrahydrofuran (THF) was chilled to -78 °C under a nitrogen atmosphere. A 2.5 M solution of n-butyl lithium (12 mL, 0.030 mol) in hexanes was added dropwise to the chilled solution. When the addition was complete, the reaction mixture was stirred at -78 °C for about 45 minutes. Trimethylborate (8.5 mL, 0.0748) was introduced via syringe. The reaction mixture was then allowed to warm to room temperature overnight. The room temperature solution was treated successively with 10% aqueous sodium hydroxide solution (50 mL) and water (33.5 mL) and stirred at room temperature for 1 hour. The reaction mixture was lowered to about pH = 4-5 using 10% aqueous citric acid and the THF was removed under reduced pressure. The aqueous residue was saturated with sodium chloride and extracted with ethyl acetate. The organic extract was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to provide a white solid which was washed with hexanes to provide the product as a white solid (yield: 1.5 g; 36%). M.p. 170 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 2.47 (s, 3H), 7.20 (d, J = 8 Hz, 2H), 7.71 (d, J = 8 Hz, 2H), 7.96 (br s, 2H).

Example 2

2-Benzyl-4,5-dibromo-3(2H)-pyridazinone

Benzyl bromide (0.59 mL, 0.005 mol) was added to a stirred solution of 4,5-dibromo-3(2H)-pyridazinone (1.27 g, 0.005 mol) and potassium carbonate (0.76 g, 0.0055 mol) in 20 mL of anhydrous dimethylformamide (DMF). The solution was stirred overnight at room temperature, and partitioned between aqueous citric acid and ethyl acetate. The aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to provide a beige solid, which was purified by column chromatography (silica gel, 9:1 hexanes/ethyl acetate). The product was obtained as a white solid (yield: 1.32 g, 76.7%). M.p. 95-96 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 5.31 (s, 2H), 7.29-7.37 (m, 3H), 7.41-7.47 (m, 2H), 7.79 (s, 1H). MS (DCI-NH_3) m/z 345 $(M+H)^+$. IR (KBr) 1645 cm^{-1}.

Example 3

2-Benzyl-4-bromo-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone

A solution of the boronic acid (0.318 g, 0.001889 mol), prepared according to the method of Example 1, the dibromopyridazinone (0.975 g, 0.002834 mol), prepared according to the method of Example 2, and tetrakis(triphenylphosphine)-palladium (0) (0.16 g, 0.0142 mol), in dimethoxyethane (30 mL) was prepared. A 2 M aqueous solution of sodium carbonate (2.83 mL, 0.005668 mol) was added to the dimethoxyethane solution and the mixture was heated at reflux. After 16 hours, a chromatographic (TLC) check (9:1 hexanes/ethyl acetate) indicated that both starting materials were still present and a fresh aliquot of palladium catalyst was added. The reaction mixture was stirred at reflux for an additional 5 hours, allowed to cool to room temperature and stand over the weekend. The volatile materials were removed under reduced pressure and the residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure to provide an oil which was purified by column chromatography (silica gel, 95:5 hexanes/ethyl acetate). Fractions containing the desired product were combined and concentrated under reduced pressure. This material was rechromatographed (95:5 hexanes/ethyl acetate) to furnish 0.200 g of a beige solid. The solid was crystallized from ether/hexanes to provide white crystals (yield: 110 mg, 15%) M.p. 115-118 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 2.53 (s, 3H), 5.40 (s, 2H), 7.30-7.42 (m, 7 H), 7.49-7.54 (m, 2H), 7.65 (s, 1H). MS (DCI-NH_3) m/z 387 $(M+H)^+$.

Example 4

2-Benzyl-4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone

A solution of the product prepared in Example 3, (0.100 g, 0.000258 mol), 4-fluorobenzeneboronic acid (0.072 g, 0.000516 mol), tetrakis(triphenylphosphine)-palladium (0) (0.015 g, 0.000013 mol), and a 2 M aqueous solution of sodium carbonate (0.64 mL, 0.001291 mol) in 30 mL of dimethoxyethane (DME) was stirred at reflux for 16 hours. A fresh aliquot of palladium catalyst was added with an additional equivalent of the boronic acid. The reaction was maintained at reflux for 24 hours. The volatile materials were removed under reduced pressure and the residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered. The filtrate was adsorbed onto silica gel. The

silica gel/product was placed at the top of a column of silica gel and the product eluted with 93:7 hexanes/ethyl acetate. Fractions containing product were combined and concentrated under reduced pressure. The residue was purified further by a second column chromatography (silica gel, 95:5 hexanes/ethyl acetate). Fractions containing product were concentrated under reduced pressure to provide a viscous oil (yield: 0.028 g, 27%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (s, 3H), 5.39 (s, 2H), 6.95 (t, J = 9 Hz, 2H), 6.99 (d, J = 9 Hz, 2H), 7.11 (d, J = 9 Hz, 2H), 7.16-7.23 (m, 2H), 7.30-7.40 (m, 3H), 7.52-7.57 (m, 2H), 7.86 (s, 1H). MS (DCI-NH_3) m/z 403 $(M+H)^+$.

Example 5

2-Benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A solution of *meta*-chloroperoxybenzoic acid (MPCBA) (0.039 g, 0.00013 mol) in dichloromethane (5 mL) was added dropwise to a stirred solution of the sulfide (0.027 g, 0.000067 mol), prepared according to the method of Example 4, in chilled (0 °C) dichloromethane (10 mL). After 5 minutes, TLC (1:1 hexanes/ethyl acetate) indicated that the starting sulfide had been consumed. The reaction was quenched with aqueous sodium sulfite. The organic layer was washed twice with aqueous sodium hydroxide and once with brine. The dichloromethane solution was dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 7:3 hexanes/ethyl acetate) to provide the desired sulfone product. Further elution with 100% ethyl acetate removed the sulfoxide from the column. The sulfoxide product was re-subjected to the MCPBA oxidant (0.04 g, 1 hour, 0 °C) and worked-up as described above. The residue obtained was combined with the sulfone from the first column and the mixture was purified by column chromatography (silica gel, 7:3 hexanes/ethyl acetate). Fractions containing product were combined and concentrated under reduced pressure. The residue was crystallized from ether/hexanes to provide the product as white crystals (yield: 13 mg, 44.6%). M.p. 101-103 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.05 (s, 3H), 5.40 (s, 2H), 6.95 (t, J = 9 Hz, 2H), 7.12-7.20 (m, 2H), 7.28-7.41 (m, 3H), 7.31 (d, J = 9 Hz, 2H), 7.58-7.53 (m, 2H), 7.84 (s, 1H), 7.87 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 435 $(M+H)^+$. MS (FAB, high res.) calculated: m/z 435.1179 $(M+H)^+$, found: m/z 435.1184 $(M+H)^+$.

Example 6

2-Benzyl-4-(4-fluorophenyl)-5-methoxy-3(2H)-pyridazinone

To a mixture of 2-benzyl-5-methoxy-4-bromo-3(2H)-pyridazinone, prepared according to the method of S. Cho *et al.* described in *J. Het. Chem.*, **1996**, ***33***, 1579-1582, , (2.94 g; 10 mmol), 4-fluorobenzeneboronic acid (1.54 g; 11 mmol), and CsF (3.04 g; 22 mmol) in 25 mL of anhydrous DME, under N_2, was added $Pd(Ph_3P)_4$ (347 mg 0.3 mmol). After addition, the mixture was heated at reflux for at 100 °C, for 18 hours. The mixture was concentrated *in vacuo* and the residue partitioned between ethyl acetate and water. The acetate layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The solid residue was suspended in ethyl ether-hexanes and filtered to provide a solid product (yield: 3.1 g; about 100%; > 95% purity). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (s, 3H), 5.36 (s, 2H), 7.09 (t, J = 9 Hz, 2H), 7.31 (m, 3H), 7.50 (m, 4H), 7.91 (s, 1H). MS (DCI-NH_3) m/z 311 $(M+H)^+$, 328 $(M+NH_4)^+$.

Example 7

2-Benzyl-4-(4-fluorophenyl)-5-hydroxy-3(2H)-pyridazinone

A mixture of the product prepared according to the method of Example 6 (1.24 g; 4 mmol) in 20 mL of acetic acid was treated with aqueous 48% HBr (25 mL). The mixture was heated at reflux for about 5 to about 8 hours (TLC analysis). The mixture was concentrated *in vacuo*. The product was dissolved in ethyl acetate, washed with 10% bicarbonate, brine and concentrated *in vacuo*. The residue was treated with diethyl ether-hexanes (2:1) and the solid was filtered to provide an almost pure product (yield: 1.16 g; 98%) . ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.24 (2H), 7.21 (m, 2H), 7.30 (m, 5H), 7.55 (m, 2H), 7.85 (s, 1H), 11.31 (broad s, 1H). MS (DCI-NH_3) m/z 296 $(M+H)^+$, 314 $(M+NH_4)^+$.

Example 8

2-Benzyl-4-(4-fluorophenyl)-5-(trifluoromethylsulfonyloxy)-3(2H)-pyridazinone

A solution of the product prepared according to the method of Example 7, (89 mg, 0.3 mmol) in 2.5 mL of anhydrous pyridine was prepared under a N_2 atmosphere and maintained at 0 °C. Triflic anhydride (Tf_2O; 0.06 mL; 0.32 mmol) was added to the solution, dropwise. The resulting mixture was stirred at 0 °C for 5 minutes and at room temperature for 16 hours. (The pyridine and Tf_2O should be pure for good results. Occasionally an additional amount of Tf_2O is necessary to force the reaction to completion.) The mixture was then poured to a cold solution of

citric acid and extracted with ethyl acetate to obtain an almost pure product (yield: 127 mg, about 99%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.34 (s, 2H), 7.35 (m, 7H), 7.60 (m, 2H), 8.48 (s, 1H). MS (DCI-NH_3) m/z 429 (M+H)+, 446 $(M+NH_4)^+$.

Example 9

2-Benzyl-4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone

A mixture of the product prepared according to the method of Example 8 (154 mg, 0.36 mmol), 4-(methylthio)benzeneboronic acid (67 mg, 0.4 mmol), Et_3N (0.11 mmol; 0.8 mmol) and $Pd(Ph_3P)_4$ (30 mg, 0.025 mmol) in 15 mL of toluene was heated at reflux, about 100 °C for about 45 minutes. The mixture was concentrated *in vacuo* and the residue purified by column chromatography (hexanes-ethyl acetate 3:1) to provide the title compound (yield: 98 mg, 68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.47 (s, 3H), 5.38 (s, 2H), 6.98 (m, 4H), 7.12 (m, 2H), 7.20 (m, 2H), 7.35 (m, 3H), 7.54 (m, 2H), 7.86 (s, 1H). MS (DCI-NH_3) m/z 403 $(M+H)^+$, 420 $(M+NH_4)^+$.

Example 10

2-Benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

To a solution of the product prepared according to the method of Example 9 (140 mg, 0.348 mmol), in 10 mL of CH_2Cl_2, at 0 °C was added peracetic acid (CH_3COOOH; 0.5 mL; 30%). The mixture was stirred at 0 °C for 90 minutes. The dichloromethane was then removed *in vacuo*. The residue was dissolved in ethyl acetate, washed with 10% $NaHCO_3$, and brine. The ethyl acetate was removed under reduced pressure. The residue was chromatographed (silica gel, CH_2Cl_2-diethyl ether 19:1) to provide the title compound (yield: 130 mg, 86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.04 (s, 3H), 5.40 (s, 2H), 6.95 (m, 2H), 7.16 (m, 2H), 7.33 (m, 5H), 7.55 (m, 2H), 7.86 (m, 3H). MS (DCI-NH_3) m/z 434 $(M+H)^+$, 452 $(M+NH_4)^+$.

Example 11

4-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A mixture of the product prepared according to the method of Example 10 (37 mg, 0.085 mmol) and $AlBr_3$ (70 mg, 0.26 mmol) in 10 mL of toluene was heated at reflux, about 80 °C for about 15 minutes and cooled to 0 °C. The cooled mixture was treated with 1N HCl and extracted with ethyl acetate. The acetate layer was washed with water, brine and concentrated *in vacuo*. Purification of the residue on silica gel column (ethyl acetate as an eluent) provided the title compound (yield: 22

mg, 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.07 (s, 3H), 7.00 (t, J = 9 Hz, 2H), 7.20 (m, 2H), 7.56 (d, J = 9 Hz, 2H), 7.86 (s, 1H), 7.91 (d, J = 9 Hz, 2H), 10.94 (broad s, 1H). MS (DCI-NH_3) m/z 345 $(M+H)^+$, 362 $(M+NH_4)^+$.

Example 12

2-Phenyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

12A. 2-Phenyl-4-chloro-5-methoxy-3(2H)-pyridazinone

The 2-phenyl-4-chloro-5-methoxy-3(2H)-pyridazinone compound was prepared according to the method of S. Cho *et al.* described in *J. Het. Chem.*, **1996**, *33*, 1579-1582, , starting with the N-phenyl-dichloropyridazinone. A mixture of 2-phenyl-4,5-dichloro-3(2H)-pyridazinone (1 g, 4.1 mmol) and finely powdered, anhydrous K_2CO_3 (580 mg, 4.2 mmol) in 50 mL of methanol was heated at reflux for 5 hours and concentrated *in vacuo*. The residue was partitioned between water and ethyl acetate. The acetate layer was washed with water, and brine to provide 2-phenyl-4-chloro-5-methoxy-3(2H)-pyridazinone (yield: 920 mg, 95%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.15 (s, 3H), 7.50 (m, 5H), 8.43 (s, 1H). MS (DCI-NH_3) m/z 237 $(M+H)^+$, 254 $(M+NH_4)^+$.

12B. 2-Phenyl-4-(4-fluorophenyl)-5-methoxy-3(2H)-pyridazinone

The 2-phenyl-4-chloro-5-methoxy-3(2H)-pyridazinone product was coupled with 4-fluorophenylboronic acid according to the method of Example 6 to provide 2-phenyl-4-(4-fluorophenyl)-5-methoxy-3(2H)-pyridazinone (yield: 1.1 g; 96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.00 (s, 3H), 7.10 (t, J = 9 Hz, 2H), 7.45 (m, 3H), 7.60 (m, 4H), 8.06 (s, 1H). MS (DCI-NH_3) m/z 297 $(M+H)^+$.

12C. 2-Phenyl-4-(4-fluorophenyl)-5-hydroxy-3(2H)-pyridazinone

The 2-phenyl-4-(4-fluorophenyl)-5-methoxy-3(2H)-pyridazinone product was treated with 48% HBr according to the method of Example 7 to furnish 2-phenyl-4-(4-fluorophenyl)-5-hydroxy-3(2H)-pyridazinone (yield: 957 mg, 92%). MS (DCI-NH_3) m/z 283 $(M+H)^+$, 300 $(M+NH_4)^+$.

12D. 2-Phenyl-4-(4-fluorophenyl)-5-trifluoromethanesulfonyloxy-3(2H)-pyridazinone

The 2-phenyl-4-(4-fluorophenyl)-5-hydroxy-3(2H)-pyridazinone product was sulfonylated according to the method of Example 8 to furnish 2-phenyl-4-(4-fluorophenyl)-5-trifluoromethanesulfonyloxy-3(2H)-pyridazinone (yield: 1.35 g; 96%) MS (DCI-NH_3) m/z 415 $(M+H)^+$, 432 $(M+NH_4)^+$.

12E. 2-Phenyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The 2-phenyl-4-(4-fluorophenyl)-5-trifluoromethanesulfonyloxy-3(2H)-pyridazinone was coupled with 4-(methylthio)phenylboronic acid as in Example 9 to provide 2-phenyl-4-(4-Fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (yield: 915 mg, 92%) which was immediately oxidized with peracetic acid as in Example 9 to provide the title compound after column chromatography (silica gel, 1:1 hexanes-ethyl acetate) and crystallization from diethyl ether-hexanes (yield: 288 mg, 69%). M.p. 219-220 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.25 (s, 3H), 7.15 (t, J = 9 Hz, 2H), 7.30 (m, 2H), 7.46 (m, 1H), 7.56 (m, 4H), 7.64 (m, 2H), 7.90 (d, J = 9 Hz, 2H), 8.24 (s, 1H). MS (DCI-NH_3) m/z 421 $(M+H)^+$, 438 $(M+NH_4)^+$.

Example 13

4-Fluorophenylacetic acid, methyl ester

A catalytic amount (0.5 mL) of concentrated sulfuric acid was added to a solution of 4-fluorophenylacetic acid (30.8 g, 0.20 mol) in 500 mL of methanol. The solution was stirred at reflux for 4 hours. The volatile materials were removed under reduced pressure to furnish a colorless oil which was dissolved in ether/ethyl acetate and washed with 2 N aqueous Na_2CO_3, brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure to provide an oil which was dried overnight under high vacuum (yield: 33.6 g; 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.59 (s, 2H), 3.65 (s, 3H), 7.01 (t, J = 9 Hz, 2H), 7.20-7.28 (m, 2H). MS (DCI-NH_3) m/z 186 $(M+NH_4)^+$.

Example 14

[4-(Methylthio)phenyl]dimethylthioketene acetal, mono-S-oxide

A mixture of methyl(methylsulfinylmethyl)sulfide (50 g, 0.40 mol), and finely powdered sodium hydroxide (3.12 g, 0.078 mol) was stirred at 70 °C for 4 hours. 4-(Methylthio)benzaldehyde (27.4 mL, 0.195 mol) was then added in one lot and the reaction mixture was stirred at 70 °C for an additional 4 hours. The mixture was cooled to room temperature and partitioned between 10% aqueous citric acid and dichloromethane. The organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to provide a brown oil. The oil was purified by column chromatography (7:3 hexanes/ethyl acetate) to provide a solid. The solid was crystallized from ether/hexanes (yield: 24.7 g; 72%). M.p. 52-53 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H), 2.53 (s, 3H), 2.77 (s, 3H), 7.17 (d,

J = 9 Hz, 2H), 7.57 (s, 1H), 7.86 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 259 $(M+H)^+$ and m/z 276 $(M+NH_4)^+$.

Example 15

2-(4-Fluorophenyl)-3-[4-(methylthio)phenyl]-4-methylthio-4-methylsulfinyl-n-butyric acid, methyl ester

A solution of the ester product, prepared according to the method of Example 13, (16.24 g, 0.0966 mol) in 50 mL of THF was added dropwise to a stirred solution of 1.0 M sodium hexamethyldisilazide in THF (96.6 mL, 0.0966 mol), maintained at 0 °C, under an atmosphere of dry nitrogen. After 30 minutes, a solution of the ketene thioacetal, prepared according to the method of Example 14 (20.8 g, 0.0805 mol), in 50 mL of THF, was added dropwise to the reaction mixture maintained at 0 °C. After 4 hours, the reaction mixture was acidified with 10% aqueous citric acid. The aqueous layer was washed twice with ethyl acetate. The organic extracts were combined, washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to provide a brown oil which was purified by column chromatography (85:15 to 1:1 dichloromethane/ethyl acetate gradient). Several products having different R_f values and NMR spectra were isolated. These compounds had identical mass spectra. The mixture of compounds was carried on in the following reactions (yield: 22.4 g; 65%). MS (DCI-NH_3) m/z 444 $(M+NH_4)^+$.

Example 16

2-(4-Fluorophenyl)-3-[4-(methylthio)phenyl]-3-formyl-n-propanoic acid, methyl ester

The mixture of compounds, prepared according to Example 17, (9.0 g, 0.021 mol) was dissolved in acetonitrile (80 mL) and cooled to 0 °C. Perchloric acid (60%; 1.06 g, 0.006 mol) was added to the stirred solution. The reaction mixture was stirred at 0 °C for 8 hours, and quenched with 2 N aqueous Na_2CO_3. The acetonitrile was removed under reduced pressure and the resulting aqueous mixture was extracted with ethyl acetate. The organic solution was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to give a yellow oil which was purified by column chromatography (silica gel, 7:3 hexanes/ethyl acetate). Fractions containing the highest Rf diastereomers from the product mixture were concentrated *in vacuo* and the residue was crystallized from methanol to furnish the title aldehyde-ester compound as white crystals (yield: 0.27 g, 4.0%). M.p. = 112-113 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 2.49 (s, 3H), 2.46 (s, 3H), 4.39 (s, 2H), 7.03 (t, J = 9 Hz, 1H), 7.21 (d, J = 9 Hz, 1H), 7.25 (d, J = 9 Hz, 2H),

7.40-7.47 (m, 2H). MS (DCI-NH_3) m/z 333 $(M+H)^+$ and m/z 350 $(M+NH_4)^+$. Fractions containing lower R_f compounds from the product mixture were concentrated *in vacuo* and the residue was identified as the hydrate of the aldehyde-ester (yield: 2.6 g, 35.2%). ^1H NMR (300 MHz, $CDCl_3$) δ 2.44 & 2.46 (2 s, 3H), 3.56 & 3.48 (2 s, 3H), 3.55 & 3.76 (2 dd, J = 6 Hz, J = 6 Hz, 1H), 3.98 & 4.26 (2 d, J = 12 Hz, 1H), 5.41 & 5.47 (2 d, J = 6 Hz, 1H), 6.96 & 7.00 (t, J = 9 Hz, 2H), 7.11-7.26 (m, 6H). MS (DCI-NH_3) m/z 333 $(M+H)^+$ and m/z 350 $(M+NH_4)^+$.

The lowest R_f compound was identified as the hydroxy lactone formed when a hydroxy group from the hydrate displaces the methoxy group from the ester (yield: 1.1 g, 16.4%). ^1H NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 3H), 3.54-3.71 (m, 1H), 3.98-4.21 (m, 1H), 4.61 (broad s, 1H), 5.85-6.01 (m, 1H), 6.98 (t, J = 9 Hz, 2H), 7.12-7.27 (m, 6H). MS (DCI-NH_3) m/z 336 $(M+NH_4)^+$.

Example 17

4-(4-Fluorophenyl)-5-[4-(methylthio)phenyl]-4,5-dihydro-3(2H)-pyridazinone

The aldehyde-ester, hydrate, and hydroxy lactone prepared in Example 16 (0.10 g, 3 mmol), were dissolved in 100 mL of ethanol. This solution was treated with hydrazine monohydrate (0.15 mL, 30 mmol) and the resulting solution was stirred at reflux in a Soxhelet apparatus containing molcular sieves. After 18 hours, the reaction mixture was cooled and the volatile materials removed under reduced pressure. The residue was partitioned between ethyl acetate and aqueous HCl. The aqueous layer was washed twice with ethyl acetate. The combined organic extracts were washed twice with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (4:1 hexanes/ethyl acetate) to obtain the title compound (yield: 50 mg, 53%). ^1H NMR (300 MHz, $CDCl_3$) δ 2.46 (s, 3H), 3.75 (d, J = 12 Hz, 1H), 3.87 (d, J = 12 Hz, 1H), 6.93-7.08 (m, 6H), 7.16 (d, J = 9 Hz, 2H), 8.71 ($s_{(broad)}$, 1H). MS (DCI-NH_3) m/z 315 $(M+H)^+$ and m/z 332 $(M+NH_4)^+$.

Example 18

4-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-4,5-dihydro-3(2H)-pyridazinone

A solution of peracetic acid, 32% in acetic acid, (0.4 mL, 1.6 mmol) was added to a stirred solution of the sulfide, prepared according to the method of Example 17, (0.050 g, 0.16 mmol) in dichloromethane, and maintained at 0 °C. The reaction mixture was stirred for 5 hours at 0 °C then diluted with water. The organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated

under reduced pressure to provide an oil which solidified on trituration with ether (yield: 47 mg, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.05 (s, 3H), 3.77 (d, J = 12 Hz, 1H), 4.05 (d, J = 12 Hz, 1H), 6.95-7.08 (m, 4H), 7.28 (d, J = 9 Hz, 2H), 7.90 (d, J = 9 Hz, 2H), 8.75 (s, broad, 1H). MS (DCI-NH_3) m/z 364 $(M+NH_4)^+$.

Example 19

4-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The dihydropyridazinone product prepared according to the method of Example 18 (47 mg, 0.136 mmol) was dissolved in acetic acid (25 mL). Bromine (0.025 mL, 0.16 mmol) was added to the solution and the reaction mixture was stirred at 95 °C for 20 minutes. The reaction mixture was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to provide a solid which was eluted through a short pad of silica gel with ethyl acetate. The title compound was crystallized from ethyl acetate/hexanes (yield: 35 mg, 75%). M.p. 255-256 °C ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.07 (s, 3H), 6.98 (t, J = 9 Hz, 2H), 7.16-7.23 (m, 2H), 7.35 (d, J = 9 Hz, 2H), 7.86 (s, 1H), 7.91 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 345 $(M+H)^+$ and m/z 362 $(M+NH_4)^+$.

Example 20

2-(4-Fluorobenzyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A solution of the nitrogen-unsubstituted pyridazinone product, prepared in Example 19 (160 mg, 0.465 mmol), K_2CO_3 (193 mg, 1.4 mmol), 4-fluorobenzyl-bromide (0.09 mL, 0.7 mmol) and NaI (catalytic) in 10 mL of anhydrous N,N-dimethylformamide (DMF) was stirred at room temperature for 18 hours. The reaction mixture was quenched with 2N HCl, extracted with ethyl acetate (2 x 20 mL), washed with brine and water, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (2:2:6 ethyl acetate/dichloromethane/pentanes). Crystallization from ether/pentanes provided white crystals (yield: 110 mg, 52%). M.p. 153-154 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.06 (s, 3H), 5.36 (s, 2H), 6.96 (t, J = 8.4 Hz, 2H), 7.04 (t, J = 8.7 Hz, 2H), 7.16 (dd, J = 9.1 Hz, J = 5.4 Hz, 2H), 7.31 (d, J = 8.5 Hz, 2H), 7.54 (dd, J = 8.8 Hz, 5.5 Hz, 2H), 7.84 (s, 1H), 7.87 (d, J = 8.8 Hz, 2H). MS (DCI-NH_3) m/z 453 $(M+H)^+$.

Example 21

2-(Phenylpropargyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting phenylpropargyl bromide for 4-fluorobenzyl bromide. M.p. 100-103 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.06 (s, 3H), 5.26 (s, 2H), 6.97 (t, J = 9 Hz, 2H), 7.20 (dd, J = 9 Hz, J = 6 Hz, 2H), 7.31 (m, 3H), 7.34 (d, J = 9 Hz, 2H), 7.48 (m, 2H), 7.89 (d, J = 9 Hz, 2H), 7.9 (s, 1H). MS (DCI-NH_3) m/z 459 $(M+H)^+$.

Example 22

2-(2,4-Difluorobenzyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting 2,4-difluorobenzyl bromide for 4-fluorobenzyl bromide. M.p. 179-182 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.06 (s, 3H), 5.45 (s, 2H), 6.87 (m, 2H), 6.96 (t, J = 9 Hz, 2H), 7.17 (dd, J = 9 Hz, J = 6 Hz, 2H), 7.32 (d, J = 9 Hz, 2H), 7.54 (m, 1H), 7.86 (s, 1H), 7.88 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 471 $(M+H)^+$.

Example 23

2-(Methyl-2-propenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting 3-chloro-2-methylpropene for 4-fluorobenzyl bromide. M.p. 140-142 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.86 (s, 3H), 3.08 (s, 3H), 4.83 (s, 2H), 4.94 (t, J = 1 Hz, 1H), 5.05 (t, J = 1 Hz, 1H), 6.98 (t, J = 9 Hz, 2H), 7.21 (dd, J = 9 Hz, J = 6 Hz, 2H), 7.37 (d, J = 9 Hz, 2H), 7.89 (s, 1H), 7.91 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 399 $(M+H)^+$.

Example 24

2-(3-Methyl-2-butenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The desired compound was prepared according to the method of Example 20 substituting 4-bromo-2-methyl-2-butene for 4-fluorobenzyl bromide. M.p. 169-172 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.78 (s, 3H), 1.85 (s, 3H), 3.06 (s, 3H), 4.86 (d, J = 7.5 Hz, 2H), 5.47 (t, J = 7.5 Hz, 1H), 6.96 (t, J = 9 Hz, 2H), 7.18 (dd, J = 9 Hz,

J = 6 Hz, 2H), 7.33 (d, J = 9 Hz, 2H), 7.84 (s, 1H), 7.88 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 413 $(M+H)^+$.

Example 25

2-(2-Trifluoromethylbenzyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting 2-(trifluoromethyl)benzyl bromide for 4-fluorobenzyl bromide. M.p. 87-90 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.07 (s, 3H), 5.66 (s, 2H), 6.97 (t, J = 9 Hz, 2H), 7.21 (dd, J = 9 Hz, J = 6 Hz, 2H), 7.26 (d, J = 7.7 Hz 1H), 7.37 (d, J = 9 Hz, 2H), 7.42 (t J = 7.7 Hz, 1H), 7.53 (t, J = 7.7 Hz, 1H), 7.73 (d J = 7.7 Hz, 1H), 7.9 (s, 1H), 7.91 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 503 $(M+H)^+$.

Example 26

2-(Cyclopropylmethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting 2-(bromomethyl)cyclopropane for 4-fluorobenzyl bromide. M.p. 118-121 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.45-0.52 (m, 2H), 0.54-0.63 (m, 2H), 1.40-1.52 (m, 1H), 3.07 (s, 3H), 4.07 (d, J = 7 Hz, 2H), 6.97 (t, J = 9 Hz, 2H), 7.19 (dd, J = 9 Hz, J = 6 Hz, 2H), 7.35 (d, J = 9 Hz, 2H), 7.83 (s, 1H), 7.88 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 399 $(M+H)^+$ and m/z 416 $(M+NH_4)^+$.

Example 27

2-(2-Pyridylmethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting 2-(bromomethyl)pyridine for 4-fluorobenzyl bromide. M.p. 182-184 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.07 (s, 3H), 5.56 (s, 2H), 6.95 (m, 2H), 7.17 (m, 2H), 7.26 (m, 1H), 7.35 (m, 2H), 7.46 (m, 1H), 7.71 (m, 1H), 7.90 (m, 3H), 8.63 (m, 1H). MS (DCI-NH_3) m/z 436 $(M+H)^+$.

Example 28

2-(4-Pyridylmethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting 4-(bromomethyl)pyridine for 4-fluorobenzyl bromide. M.p. 153-156 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.07 (s, 3H), 5.40 (s, 2H), 6.97 (m, 2H), 7.17 (m, 2H), 7.34 (m, 2H), 7.42 (m, 2H), 7.90 (m, 3H), 8.63 (m, 2H). MS (DCI-NH_3) m/z 436 $(M+H)^+$.

Example 29

2-(3-Pyridylmethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting 3-(bromomethyl)pyridine for 4-fluorobenzyl bromide. M.p. 160-161 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.07 (s, 3H), 5.43 (s, 2H), 6.97 (m, 2H), 7.15 (m, 2H), 7.34 (m, 4H), 7.35 (m, 2H), 7.87 (m, 2H), 7.97 (s, 1H), 8.60 (m, 1H), 8.81 (m, 1H). MS (DCI-NH_3) m/z 436 $(M+H)^+$.

Example 30

2-(6-Fluoroquinolin-2-ylmethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting 2-(chloromethyl)-6-fluoroquinoline for 4-fluorobenzyl bromide. M.p. 116-119 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.07 (s, 3H), 5.73 (s, 2H), 6.96 (m, 2H), 7.18 (m, 2H), 7.34 (m, 4H), 7.35 (m, 2H), 7.46 (m, 2H), 7.58 (m, 3H), 7.90 (m, 3H), 8.12 (m, 2H). MS (DCI-NH_3) m/z 504 $(M+H)^+$.

Example 31

2-(Quinolin-2-ylmethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting 2-(chloromethyl)-quinoline for 4-fluorobenzyl bromide. M.p. 97-100 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.06 (s, 3H), 5.75 (s, 2H), 6.95 (m, 2H), 7.19 (m, 2H), 7.35 (m, 2H), 7.55 (m, 2H), 7.73 (m, 1H), 7.82 (m, 1H), 7.90 (m, 3H), 8.15 (m, 2H). MS (DCI-NH_3) m/z 386 $(M+H)^+$.

Example 32

2-Benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinethione

A mixture of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, prepared according to the method of Example 5, (109 mg, 0.25 mmol) and Lawesson's reagent (202 mg, 0.5 mmol) in 15 mL of toluene was stirred at reflux for 48 hours. The mixture was concentrated *in vacuo* and the residue was chromatographed (silica gel, ethyl acetate) to provide the title compound (yield: 100 mg, 88%). M.p. 88-90 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.04 (s, 3H), 6.05 (s, 2H), 6.96 (m, 2H), 7.08 (m, 2H), 7.26 (m, 2H), 7.37 (m, 3H), 7.61 (m, 2H), 7.84 (d, J = 9 Hz, 2H), 8.13 (s, 1H). MS (DCI-NH_3) m/z 451 $(M+H)^+$.

Example 33

2-Benzyl-4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

33A. Preparation of 2-Benzyl-4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

A solution of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone, prepared according to the method of Example 4, (450 mg, 1.12 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a suspension of hydroxy(tosyloxy)iodobenzene (439 mg, 1.12 mmol) in CH_2Cl_2 (15 mL) and the mixture was stirred until a clear solution was obtained (about 1 hour). The reaction mixture was then washed with water and dried with $MgSO_4$. Removal of solvent *in vacuo* provided the corresponding sulfoxide (yield: 485 mg, about 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.72 (s, 3H), 5.40 (s, 2H), 6.90 (m, 2H), 7.15 (m, 3H), 7.33 (m, 3H), 7.57 (m, 3H), 7.71 (m, 1H), 7.86 (s, 1H). MS (DCI-NH_3) m/z 419 $(M+H)^+$, 436 $(M+NH_4)^+$.

33B. Preparation of 2-benzyl-4-(4-fluorophenyl)-5-(acetoxymethylsulfonylphenyl)-3(2H)-pyridazinone

The sulfoxide was transformed into the sulfonamide according to a procedure described by M. De Vleeschauwer and J. V. Gauthier in *Syn. Lett.*, **1997**,*375* with the following modifications:

A suspension of the sulfoxide, prepared according to the method of Example 33A, (485 mg, 1.12 mmol) and AcONa (1.4 g) in 15 mL of Ac_2O was stirred at reflux for 2 hours and concentrated *in vacuo*. The residue was distilled twice with toluene, dissolved in 25 mL of CH_2Cl_2, cooled to 0 °C, and treated with CH_3CO_3H (1 mL). After 1 hour, the mixture was washed, successively, with saturated $NaHCO_3$ and brine. The solvent was removed *in vacuo*. The residue was

chromatographed (silica gel, 1:1 hexanes-ethyl acetate) to provide the desired product, 2-benzyl-4-(4-fluorophenyl)-5-(acetoxymethylsulfonylphenyl)-3(2H)-pyridazinone (yield: 150 mg, 27%). MS (DCI-NH_3) m/z 493 $(M+H)^+$.

33C. Preparation of 2-Benzyl-4-(4-fluorophenyl)-5-[4-(sodiumsulfinate)phenyl]-3(2H)-pyridazinone

To a solution of the acetoxymethylsulfone, prepared according to the method of Example 33B, (150 mg, 0.305 mmol), in 10 mL of THF and 5 mL of methanol at 0 °C, was added 1 N NaOH (0.305 mL, 0.305 mmol). The mixture was stirred at 0 °C for 1 hour. The mixture was concentrated *in vacuo*, the residual water was removed via an EtOH/toluene azeotrope followed by a toluene azeotrope. The residue was dried under high vacuum for 48 hours to provide the sodium sulfinate (yield: 140 mg, 96%). MS (DCI-NH_3) m/z 443 $(M+H)^+$

33D. Preparation of 2-Benzyl-4-(4-fluorophenyl)-5-[4-(chlorosulfonyl)phenyl]-3(2H)-pyridazinone

The sodium sulfinate (about 0.31 mmol) in CH_2Cl_2 (10 mL) was treated at 0 °C with $SOCl_2$ (0.033 mL, 0.4 mmol) for 2 hours. The mixture was washed with brine, dried with $MgSO_4$ and concentrated *in vacuo* to provide the crude sulfonyl chloride (yield: 145 mg, about 100%). MS (DCI-NH_3) m/z 455 $(M+H)^+$.

33E. Preparation of 2-Benzyl-4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The crude chloride prepared according to the method of Example 33D, in 10 mL of THF, was added to a solution of 50% NH_4OH, in 10 mL of THF, maintained at 0 °C. The mixture was allowed to warm to room temperature over 3.5 hours. The THF was removed *in vacuo* and the product was extracted with ethyl acetate. The ethyl acetate was removed *in vacuo* and the residue was treated with diethyl ether-hexanes 2:1 to provide the sulfonamide (yield: 113 mg, 84%). M.p. 188-191 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 2.70 (dd, J = 15 Hz, 2H), 5.36 (s, 2H), 7.13 (t, J = 9 Hz, 2H), 7.22 (m, 2H), 7.40 (m, 7H), 7.73 (d, J = 9 Hz, 2H), 8.11 (s, 1H). MS (DCI-NH_3) m/z 436 $(M+H)^+$.

Example 34

2-(2,2,2-Trifluoroethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting 2-iodo-1,1,1-trifluoroethane for 4-fluorobenzyl bromide. M.p. 177-179

°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.06 (s, 3H), 4.88 (q, J = 9 Hz, 2H), 6.98 (t, J = 9 Hz, 2H), 7.18 (dd, J = 9 Hz, J = 6 Hz, 2H), 7.35 (d, J = 9 Hz, 2H), 7.89 (s, 1H), 7.91 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 427 $(M+H)^+$ and m/z 444 $(M+NH_4)^+$.

Example 35

2-(3,3-Dichloro-2-propenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting 1,1,3-trichloropropene for 4-fluorobenzyl bromide. M.p. 150-152 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.06 (s, 3H), 4.98 (d, J = 7 Hz, 2H), 6.25 (t, J = 7 Hz, 1H), 6.98 (t, J = 9 Hz, 2H), 7.18 (dd, J = 9 Hz, J = 6 Hz, 2H), 7.33 (d, J = 9 Hz, 2H), 7.85 (s, 1H), 7.89 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 453 $(M+H)^+$ and m/z 470 $(M+NH_4)^+$.

Example 36

2-(3-Phenyl-2-propenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting cinnamyl bromide for 4-fluorobenzyl bromide. M.p. 165-167 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.06 (s, 3H), 5.01 (d, J = 7 Hz, 2H), 6.48 (dt, J = 15 Hz, 7 Hz, 1H), 6.79 (d, J = 15 Hz, 1H), 6.97 (t, J = 9 Hz, 2H), 7.19 (dd, J = 9 Hz, J = 6 Hz, 2H), 7.25-7.44 (m, 5H), 7.37 (d, J = 9 Hz, 2H), 7.86 (s, 1H), 7.89 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 461 $(M+H)^+$ and m/z 478 $(M+NH_4)^+$.

Example 37

2-(4-Carboxyphenacyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting methyl 4-(bromomethyl)benzoate for 4-fluorobenzyl bromide and hydrolysis of the resulting ester. M.p. 239-241 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.06 (s, 3H), 5.46 (s, 2H), 6.96 (t, J = 9 Hz, 2H), 7.17 (dd, J = 9 Hz, 6 Hz, 2H), 7.33 (d, J = 9 Hz, 2H), 7.63 (d, J = 9 Hz, 2H), 7.87 (s, 1H), 7.89 (d, J = 9 Hz, 2H), 8.08 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 479 $(M+H)^+$ and m/z 496 $(M+NH_4)^+$.

Example 38

2-(5-Methylthiazol-2-ylmethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting 2-(bromomethyl)-5-methylthiazole for 4-fluorobenzyl bromide. M.p. 114-116 °C. ^{1}H NMR (d_6-DMSO, 300 MHz) δ 2.64 (s, 3H), 3.23 (s, 2H), 5.37 (s, 2H), 7.13 (m, 2H), 7.23 (m, 2H), 7.40 (s, 1H), 7.47 (d, J = 8 Hz, 2H), 7.87 (d, J = 8 Hz, 2H), 8.10 (s, 1H). MS (DCI-NH_3) m/z 356 $(M+H)^+$.

Example 39

2-(5-Chlorothiazol-2-ylmethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting 2-(bromomethyl)-5-chlorothiazole for 4-fluorobenzyl bromide. M.p. 185-186 °C. ^{1}H NMR (d_6-DMSO, 300 MHz) δ 2.32 (s, 3H), 5.50 (s, 2H), 7.15 (m, 2H), 7.24 (m, 2H), 7.47 (m, 2H), 7.87 (m, 3H), 8.14 (s, 1H). MS (DCI-NH_3) m/z 476 $(M+H)^+$ and m/z 493 $(M+NH_4)^+$.

Example 40

2-(2,3,3,4,4,4-Hexafluoro-n-buten-1-yl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting 2,2,3,3,4,4,4-heptafluoro-1-iodobutane for 4-fluorobenzyl bromide. Under the alkylation conditions, elimination of HF provided the unsaturated product. M.p. 167-169 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.07 (s, 3H), 7.00 (t, J = 9 Hz, 2H), 7.17 (dd, J = 9 Hz, 6 Hz, 2H), 7.33 (d, J = 9 Hz, 2H), 7.68 (d, J = 24 Hz, 1H), 7.93 (d, J = 9 Hz, 2H), 8.01 (s, 1H). MS (DCI-NH_3) m/z 507 $(M+H)^+$ and m/z 524 $(M+NH_4)^+$.

Example 41

2-(2,4-Difluorophenacyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting 2-chloro-2',4'-difluoroacetophenone for 4-fluorobenzyl bromide. M.p. 191-192 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.08 (s, 3H), 5.57 (d, J = 3 Hz, 2H), 6.94-7.07 (m, 2H), 6.96 (t, J = 9 Hz, 2H), 7.39 (dd, J = 9 Hz, 6 Hz, 2H), 7.91 (s, 1H), 7.91

(d, J = 9 Hz, 2H), 8.03-8.12 (m, 1H). MS (DCI-NH_3) m/z 499 $(M+H)^+$ and m/z 516 $(M+NH_4)^+$.

Example 42

2-(5-Chlorothien-2-ylmethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting 2-(bromomethyl)-5-chlorothiophene for 4-fluorobenzyl bromide. M.p. 139-141 °C. ^1H NMR (d_6-DMSO, 300 MHz) δ 3.23 (s, 3H), 5.43 (s, 2H), 7.03 (d, J = 4 Hz, 1H), 7.09-7.29 (m, 5H), 7.47 (d, J = 8 Hz, 2H), 7.87 (d, J = 8 Hz, 3H), 8.13 (s, 1H). MS (DCI-NH_3) m/z 474 $(M+H)^+$ and m/z 492 $(M+NH_4)^+$.

Example 43

2-(5-Methylthien-2-ylmethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting 2-(bromomethyl)-5-methylthiophene for 4-fluorobenzyl bromide. M.p. 172-175 °C. ^1H NMR (d_6-DMSO, 300 MHz) δ 3.22 (s, 3H), 5.49 (s, 2H), 7.03 (m, 1H), 7.14 (m, 2H), 7.23 (m, 3H), 7.48 (m, 3H), 7.86 (m, 2H), 8.11 (s, 1H). MS (DCI-NH_3) m/z 441 $(M+H)^+$ and m/z 458 $(M+NH_4)^+$.

Example 44

2-(4-Diethylaminophenacyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting 2-chloro-4'-diethylaminoacetophenone for 4-fluorobenzyl bromide. M.p. 105-108 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.23 (t, J = 7 Hz, 3H), 3.07 (s, 3H), 3.44 (q, J = 7 Hz, 2H), 5.61 (s, 2H), 6.66 (d, J = 9 Hz, 2H), 6.94 (t, J = 9 Hz, 2H), 7.21 (dd, J = 9 Hz, 6 Hz, 2H), 7.38 (d, J = 9 Hz, 2H), 7.87-7.94 (m, 4H), 7.90 (s, 1H). MS (DCI-NH_3) m/z 534 $(M+H)^+$.

Example 45

2-(2,3,4,5,6-Pentafluorobenzyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting 2,3,4,5,6-pentafluorobenzyl bromide for 4-fluorobenzyl bromide. M.p.

115-116 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) 3.06 (s, 3H), 5.50 (s, 2H), 6.96 (t, J = 9 Hz, 2H), 7.17 (dd, J = 9 Hz, 6 Hz, 2H), 7.33 (d, J = 9 Hz, 2H), 7.82 (s, 1H), 7.89 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 525 $(M+H)^+$ and m/z 542 $(M+NH_4)^+$.

Example 46

2-(Phenacyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting 2-bromoacetophenone for 4-fluorobenzyl bromide. M.p. 228-230 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) 3.07 (s, 3H), 5.68 (s, 2H), 6.95 (t, J = 9 Hz, 2H), 7.20 (dd, J = 9 Hz, 6 Hz, 2H), 7.38 (d, J = 9 Hz, 2H), 7.53 (t, J = 7 Hz, 2H), 7.65 (t, J = 7 Hz, 1H), 7.90 (d, J = 9 Hz, 2H), 7.91 (s, 1H), 8.04 (d, J = 7 Hz, 2H). MS (DCI-NH_3) m/z 463 $(M+H)^+$ and m/z 480 $(M+NH_4)^+$.

Example 47

2-(4-Chlorophenacyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting 2-bromo-4'-chloroacetophenone for 4-fluorobenzyl bromide. M.p. 186-188 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) 3.07 (s, 3H), 5.63 (s, 2H), 6.95 (t, J = 9 Hz, 2H), 7.19 (dd, J = 9 Hz, 6 Hz, 2H), 7.38 (d, J = 9 Hz, 2H), 7.51 (d, J = 9 Hz, 2H), 7.65 (t, J = 7 Hz, 1H), 7.90 (d, J = 9 Hz, 2H), 7.91 (s, 1H), 7.98 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 497 $(M+H)^+$ and m/z 514 $(M+NH_4)^+$.

Example 48

2-(Propargyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting propargyl bromide for 4-fluorobenzyl bromide. M.p. 196-198 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) 2.42 (t, J = 3 Hz, 1H), 3.06 (s, 3H), 5.04 (d, J = 3 Hz, 2H), 6.97 (t, J = 9 Hz, 2H), 7.19 (dd, J = 9 Hz, 6 Hz, 2H), 7.34 (d, J = 9 Hz, 2H), 7.90 (s, 1H), 7.91 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 383 $(M+H)^+$ and m/z 400 $(M+NH_4)^+$.

Example 49

<u>2-(4-Cyanophenacyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone</u>

The title compound was prepared according to the method of Example 20, substituting 2-bromo-4'-cyanoacetophenone for 4-fluorobenzyl bromide. M.p. 188-189 °C. ^1H NMR ($CDCl_3$, 300 MHz) 3.08 (s, 3H), 5.64 (s, 2H), 6.96 (t, J = 9 Hz, 2H), 7.19 (dd, J = 9 Hz, 6 Hz, 2H), 7.38 (d, J = 9 Hz, 2H), 7.84 (d, J = 9 Hz, 2H), 7.91 (d, J = 9 Hz, 2H), 7.93 (s, 1H), 8.14 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 488 $(M+H)^+$.

Example 50

<u>2-(α-Methyl-4-fluorobenzyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone</u>

The title compound was prepared according to the method of Example 20, substituting α-methyl-4-fluorobenzyl bromide for 4-fluorobenzyl bromide. M.p. 162-164 °C. ^1H NMR ($CDCl_3$, 300 MHz) 3.06 (s, 3H), 6.40 (t, J = 9 Hz, 2H), 6.95 (t, J = 9 Hz, 2H), 7.05 (t, J = 9 Hz, 2H), 7.15 (dd, J = 9 Hz and 6 Hz, 2H), 7.31 (d, J = 9 Hz, 2H), 7.53 (dd, J = 9 Hz and 6 Hz, 2H), 7.87 (d, J = 9 Hz, 2H), 7.88 (s, 1H). MS (DCI-NH_3) m/z 467 $(M+H)^+$ and m/z 484 $(M+NH_4)^+$.

Example 51

<u>2-Phenethyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone</u>

The title compound was prepared according to the method of Example 20, substituting (2-bromoethyl)benzene for 4-fluorobenzyl bromide. M.p. 170-171 °C. ^1H NMR ($CDCl_3$, 300 MHz) 3.07 (s, 3H), 3.20 (t, J = 9 Hz, 2H), 4.28 (t, J = 9 Hz, 2H), 6.98 (t, J = 9 Hz, 2H), 7.18 (dd, J = 9 Hz and 6 Hz, 2H), 7.22-37 (m, 5 H), 7.34 (d, J = 9 Hz, 2H), 7.83 (s, 1H), 7.89 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 449 $(M+H)^+$ and m/z 466 $(M+NH_4)^+$.

Example 52

<u>2-Benzyl-4-(3-chloro-4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone</u>

The title compound was prepared according to the method described in Examples 6-10 substituting 3-chloro-4-fluorobenzeneboronic acid for 4-fluoro-benzeneboronic acid in Example 6. M.p. 134-136 °C. ^1H NMR ($CDCl_3$, 300 MHz) 3.06 (s, 3H), 5.41 (s, 2H), 6.96-7.02 (m, 2H), 7.29-7.41 (m, 3H), 7.33 (d, J = 9 Hz,

2H), 7.51-7.56 (m, 2H), 7.85 (s, 1H), 7.91 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 469 $(M+H)^+$ and m/z 486 $(M+NH_4)^+$.

Example 53

2-Benzyl-4-(4-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method described in Examples 6-10 except substituting 4-chlorobenzeneboronic acid for 4-fluoro-benzeneboronic acid in Example 6. M.p. 157-159 °C. ^1H NMR ($CDCl_3$, 300 MHz) 3.05 (s, 3H), 5.40 (s, 2H), 7.11 (d, J = 9 Hz, 2H), 7.24 (d, J = 9 Hz, 2H), 7.28-7.40 (m, 2H), 7.31 (d, J = 9 Hz, 2H), 7.51-7.57 (m, 2H), 7.84 (s, 1H), 7.88 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 451 $(M+H)^+$ and m/z 468 $(M+NH_4)^+$.

Example 54

2-(2,2,2-Trifluoroethyl)-4-(3-chloro-4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared by N-debenzylation of the product, prepared in Example 52 according to the method of Example 11, followed by alkylation with 2-iodo-1,1,1-trifluoroethane according to the method of Example 20. M.p. 165-166 °C. ^1H NMR ($CDCl_3$, 300 MHz) 3.07 (s, 3H), 4.89 (q, J = 9 Hz, 2H), 7.00-7.06 (m, 2H), 7.31-7.35 (m, 1H), 7.37 (d, J = 9 Hz, 2H), 7.90 (s, 1H), 7.94 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 461 $(M+H)^+$ and m/z 478 $(M+NH_4)^+$.

Example 55

2-(4-Trifluoromethoxyphenacyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting 2-bromo-4'-trifluoromethoxyacetophenone for 4-fluorobenzyl bromide. M.p. 160-161 °C. ^1H NMR ($CDCl_3$, 300 MHz) 3.08 (s, 3H), 5.65 (s, 2H), 6.96 (t, J = 9 Hz, 2H), 7.20 (dd, J = 9 Hz, 6 Hz, 2H), 7.37 (d, J = 9 Hz, 2H), 7.91 (d, J = 9 Hz, 2H), 7.93 (s, 1H), 8.11 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 547 $(M+H)^+$ and m/z 564 $(M+NH_4)^+$.

Example 56

2-(4-Trifluoromethylphenacyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting 2-bromo-4'-trifluoromethylacetophenone for 4-fluorobenzyl bromide. M.p. 205-206 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) 3.07 (s, 3H), 5.66 (s, 2H), 6.96 (t, J = 9 Hz, 2H), 7.20 (dd, J = 9 Hz, 6 Hz, 2H), 7.38 (d, J = 9 Hz, 2H), 7.80 (d, J = 9 Hz, 2H), 7.91 (d, J = 9 Hz, 2H), 7.92 (s, 1H), 8.15 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 531 $(M+H)^+$ and m/z 548 $(M+NH_4)^+$.

Example 57

2-[2-(Benzo[b]thien-3-yl)-2-oxoethyl]-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting 3-chloroacetylbenzo[b]thiophene for 4-fluorobenzyl bromide. M.p. 183-184 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) 3.08 (s, 3H), 5.68 (s, 2H), 6.96 (t, J = 9 Hz, 2H), 7.21 (dd, J = 9 Hz, 6 Hz, 2H), 7.39 (d, J = 9 Hz, 2H), 7.42-7.54 (m, 2H), 7.91 (d, J = 9 Hz, 2H), 7.91 (d, J = 7 Hz, 1H), 7.94 (s, 1H), 8.53 (s, 1H), 8.72 (d, J = 7 Hz, 1H). MS (DCI-NH_3) m/z 519 $(M+H)^+$.

Example 58

2-(2,2,2-Trifluoroethyl)-4-(4-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared by N-debenzylation of the product, prepared in Example 54 according to the method of Example 12, followed by alkylation with 2-iodo-1,1,1-trifluoroethane according to the method of Example 20. M.p. 55-57 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) 3.07 (s, 3H), 4.88 (q, J = 9 Hz, 2H), 7.13 (d, J = 9 Hz, 2H), 7.26 (d, J = 9 Hz, 2H), 7.36 (d, J = 9 Hz, 2H), 7.89 (s, 1H), 7.92 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 443 $(M+H)^+$ and m/z 460 $(M+NH_4)^+$.

Example 59

2-(3,3-Dimethyl-2-oxobutyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting 1-bromopinacolone for 4-fluorobenzyl bromide. M.p. 168-170 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) 1.31 (s, 9H), 3.06 (s, 3H), 5.21 (s, 2H), 6.95 (t, J = 9 Hz,

2H), 7.17 (dd, J = 9 Hz, 6 Hz, 2H), 7.35 (d, J = 7 Hz, 2H), 7.86 (s, 1H) 7.89 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 443 $(M+H)^+$ and m/z 460 $(M+NH_4)^+$.

Example 60

2-(3-Thienylmethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting 3-(chloromethyl)thiophene for 4-fluorobenzyl bromide. M.p. 169-172 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 3.22 (s, 3H), 5.36 (s, 2H), 7.18 (m, 5H), 7.51 (m, 4H), 7.88 (m, 2H); 8.08 (s, 1H). MS (DCI-NH_3) m/z 441 $(M+H)^+$ and m/z 458 $(M+NH_4)^+$.

Example 61

2-(2-Benzo[b]thienylmethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20 substituting 2-(chloromethyl)benzo[b]thiophene for 4-fluorobenzyl bromide. M.p. 93-96 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.05 (s, 3H), 5.64 (s, 2H), 6.97 (m, 2H), 7.18 (m, 2H), 7.33 (m, 5H), 7.78 (m, 2H), 7.86 (m, 3H). MS (DCI-NH_3) m/z 491 $(M+H)^+$ and m/z 508 $(M+NH_4)^+$.

Example 62

2,4-Bis(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A mixture of 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (172 mg, 0.5 mmol), prepared according to the method of Example 10, Cu powder (32 mg), anhydrous K_2CO_3 (207 mg, 1.5 mmol) and 4-fluoroiodobenzene (0.12 mL, 1 mmol) was prepared in 20 mL of pyridine . The solution was stirred at reflux for 14 hours. The mixture was then cooled to room temperature and partitioned between water and ethyl acetate. The ethyl acetate layer was washed with 10% citric acid, water, brine and concentrated *in vacuo.* Separation by column chromatography (silica gel, CH_2Cl_2-diethyl ether 15:1) provided 190 mg of crude product. Crystallization from CH_2Cl_2-diethyl ether-hexanes furnished the title compound (yield: 175 mg, 79.9%). M.p. 168-169 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.07 (s, 3H), 6.98 (t, J = 9 Hz, 2H), 7.20 (m, 4H), 7.40 (d, J = 9 Hz, 2H), 7.69 (m, 2H), 7.92 (d, J = 9 Hz, 2H), 7.98 (s, 1H). MS (DCI-NH_3)

m/z 439 $(M+H)^+$, 456 $(M+NH4)^+$. Anal. calc. for $C_{23}H_{16}F_2N_2O_3S{\cdot}0.25\ H_2O$: C, 62.36; H, 3.75; N, 6.32. Found: C, 62.23; H, 3.55; N, 6.26.

Example 63

4-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-6-methyl-3(2H)-pyridazinone

The 5-hydroxy-5-methyl-2(5H)-furanone prepared via above cited methods (454 mg, 1.25 mmol) was dissolved in n-butanol (10 mL) and treated with hydrazine hydrate (0.3 mL, 6.2 mmol) and stirred at reflux for 18 hours. On cooling, white crystals (224 mg, 50%) were obtained. M.p. 290 °C (dec.) ^{1}HNMR (300 MHz, d_6-DMSO) δ 1.99 (s, 3H), 3.10 (s, 3H), 7.05 (t, J = 9 Hz, 2H), 7.15 (dd, J = 6 Hz, J = 9 Hz, 2H), 7.48 (d, J = 9 Hz, 2H), 7.85 (d, J = 9 Hz, 2H), 13.10 (br s, 1H). MS (DCI/NH_3) 376 $(M+NH_4)^+$. Anal. calc. for $C_{18}H_{15}N_2FSO_3$ 0.25 H_2O: C, 59.57; H, 4.30; N, 7.71. Found: C, 59.28; H, 4.39; N, 8.39

Example 64

2-(2,2,2-Trifluoroethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-6-methyl-3(2H)-pyridazinone

The product of Example 63 (100 mg, 0.28 mmol) was dissolved in anhydrous DMF (3 mL) and treated with 1,1,1-trifluoro-2-iodoethane (27.5 mL, 280 mmol) in presence of anhydrous sodium carbonate (130 mg, 1.2 mmol) at 50-60 ^{o}C for 2 hours. The reaction mixture was partitioned between water and ethyl acetate to provide the desired compound as an amorphous solid (60 mg, 48%). ^{1}HNMR (300 MHz, $CDCl_3$) δ 2.10 (s, 3H), 3.10 (s, 3H), 4.85 (q, J = 9 Hz, 2H), 6.90 (m, 2H), 7.10 (dd, J = 6 Hz, J = 9 Hz, 2H), 7.25 (m, 2H), 7.95 (d, J = 9 Hz, 2H),. MS (DCI/NH_3) 458 $(M+NH_4)^+$ Anal. calc. for $C_{20}H_{16}N_2F_4SO_3$: C, 54.54; H, 3.66; N, 6.36. Found: C, 54.41; H, 3.56; N, 6.35.

Example 65

2-Benzyl-4-(3,4-dichlorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared by coupling 3,4-dichlorophenylboronic acid with 2-benzyl-4-bromo-5-methoxy-3(2H)-pyridazinone (*J. Het. Chem.*, **1996**, *33*, 1579-1582) according to the method of Example 6. This product was converted to the 5-hydroxy-derivative according to the method of Example 7. The 5-hydroxy compound was converted to the 5-trifluoromethylsufonyloxy-derivative according to the method of Example 8. Coupling of 4-(methylthio)phenylboronic acid to the triflate according to the method of Example 9 provided the 5-[4-(methylthio)phenyl]-

intermediate which was oxidized according to the method of Example 10 to provide the final product (yield: 780 mg, 84%). M.p. 161-163 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.22 (s, 3H), 5.35 (s, 2H), 7.08 (dd, J = 9 Hz, 3 Hz, 1H), 7.32-7.44 (m, 5H), 7.47 (dd, J = 9 Hz, 3 Hz, 3H), 7.48 (d, J = 3 Hz, 1H), 7.90 (d, J = 9 Hz, 2H), 8.13 (s, 1H). MS (DCI-NH_3) m/z 485 $(M+H)^+$. Anal. calc. for $C_{24}H_{18}Cl_2N_2O_3S$: C, 59.38; H, 3.73; N, 5.77. Found: C, 59.28; H, 3.92; N, 5.42.

Example 66

2-(2,2,2-Trifluoroethyl)-4-(4-n-propylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared by coupling 4-(n-propyl)phenylboronic acid with 2-benzyl-4-bromo-5-methoxy-3(2H)-pyridazinone (*J. Het. Chem.*, **1996**, *33*, 1579-1582) according to the method of Example 6. This product was converted to the 5-hydroxy- derivative according to the method of Example 7. This product was converted to the 5-trifluoromethylsufonyloxy-derivative according to the method of Example 8. Coupling of 4-(methylthio)phenylboronic acid to the triflate according to the method of Example 9 provided the 5-[4-(methylthio)phenyl]-intermediate which was oxidized according to the method of Example 10 to provide the final product (yield: 220 mg, 70%). M.p. 64-66 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, J = 7.5 Hz, 3H), 1.6 (h, J = 7.5 Hz, 2H), 2.55 (q, J = 7.5 Hz, 2H), 3.05 (s, 3H), 4.88 (q, J = 9 Hz, 2H), 7.08 (s, 4H), 7.35 (d, J = 9 Hz, 2H), 7.86 (d, J = 9 Hz, 2H), 7.87 (s, 1H). MS (DCI-NH_3) m/z 451 $(M+H)^+$. Anal. calc. for $C_{22}H_{21}F_3N_2O_3S$: C, 58.65; H, 4.69; N, 6.21. Found: C, 58.71; H, 4.72; N, 6.20.

Example 67

2-(2,2,2-Trifluoroethyl)-4-(4-chloro-3-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared by first coupling 3-fluoro-4-chlorophenylboronic acid with 2-benzyl-4-chloro-5-methoxy-3(2H)-pyridazinone according to the method of Example 6. The product was converted to the 5-hydroxy compound according to the method of Example 7. This 5-hydroxy compound was converted to the 5-trifluoromethylsufonyloxy-derivative according to the method of Example 8. Coupling of 4-(methylthio)phenylboronic acid to the triflate according to the method of Example 9 provided the 5-[4-(methylthio)phenyl]-intermediate which was oxidized according to the method of Example 10 to provide the final product (yield: 170 mg, 84%). M.p. 174-175 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.09 (s, 3H),

4.89 (q, J = 9 Hz, 2H), 6.87 (dm, J = 9 Hz, 1H), 7.09 (dd, J = 9 Hz, 3 Hz, 1H), 7.30 (t, J = 9 Hz, 1H), 7.39 (d, J = 9 Hz, 2H), 7.91 (s, 1H), 7.95 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 461 $(M+H)^+$. Anal. calc. for $C_{19}H_{13}ClF_4N_2O_3S$: C, 49.52; H, 2.84; N, 6.07. Found: C, 49.66; H, 2.70; N, 5.96.

Example 68

2-(2,2,2-Trifluoroethyl)-4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

A solution of 2-(2,2,2-trifluoroethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfinyl)-phenyl]-3(2H)-pyridazinone (680 mg, 1.53 mmol) in trifluoroacetic anhydride (30 mL) was stirred at room temperature for 1 hour. The excess solvent was evaporated *in vacuo* and the residue was treated with a deoxygenated 1N solution of methanol-NaOH (50 mL, 4:1) at 0 °C. The solution was stirred at room temperature for 2 hours and quenched with dilute HCl solution until acidic. The white suspension formed was concentrated *in vacuo* to evaporate the methanol. THF was added to the resulting suspension until a clear solution was obtained. Chlorine gas was slowly bubbled into the solution, maintained at 0 °C. After 10 minutes, nitrogen gas was bubbled into the solution for a few minutes to displace residual chlorine. Ammonium hydroxide solution (30%, 5 to 10 mL), at 0 °C, was slowly added to the solution (to consume all starting sulfonyl chloride) and stirred at room temperature for 5 minutes The solution was partitioned between water and ethyl acetate. The organic layer was washed first with water, then brine, and dried over $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by chromatography on silica gel (40:60 ethyl acetate/hexanes) to provide the title compound (yield: 500 mg, 75%). M.p. 193-195 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 4.82 (s, 2H), 4.88 (q, J = 9 Hz, 2H), 6.98 (t, J = 9 Hz, 2H), 7.19 (dd, J = 9 Hz, 6 Hz, 2H), 7.30 (d, J = 9 Hz, 2H), 7.88 (d, J = 9 Hz, 2H), 7.90 (s, 1H). MS (DCI-NH_3) m/z 428 $(M+H)^+$. Anal. calc. for $C_{18}H_{13}F_4N_3O_3S$: C, 50.58; H, 3.06; N, 9.83. Found: C, 51.04; H, 3.26; N, 9.63.

Example 69

2-(2,2,2-Trifluoroethyl)-4-(4-chlorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

69A. 2-Benzyl-4-chloro-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 77. The product was coupled with 4-chlorophenylboronic acid following the method of

Example 6. The product was N-debenzylated according to the method of Example 11 and N-alkylated with 2-iodo-1,1,1-trifluoroethane according to the method of Example 20 to provide the sulfice compound.

69B. 2-Benzyl-4-chloro-5-[4-(methylsulfinyl)phenyl]-3(2H)-pyridazinone

The sulfide was oxidized to the corresponding sulfoxide with one equivalent of *meta*-chloroperoxybenzoic acid to provide the corresponding methylsulfoxide which was converted to the sulfonamide final product according to the method of Example 68 (yield: 540 mg, 70%). M.p. 154-156 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.86 (s, 2H), 4.87 (q, J = 9 Hz, 2H), 7.14 (d, J = 9 Hz, 2H), 7.29 (d, J = 9 Hz, 2H), 7.31 (d, J = 9 Hz, 2H), 7.89 (d, J = 9 Hz, 2H), 8.00 (s, 1H). MS (DCI-NH_3) m/z 444 $(M+H)^+$. Anal. calc. for $C_{18}H_{13}ClF_3N_3O_3S$: C, 48.71; H, 2.95; N, 9.46. Found: C, 49.05; H, 3.01; N, 9.15.

Example 70

2-(2,2,2-Trifluoroethyl)-4-(2-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The methyl sulfide intermediate prepared in Example 83 was oxidized with one equivalent of *meta*-chloroperoxybenzoic acid to provide the methylsulfoxide which was converted to the sulfonamide final product according to the method of Example 68 (yield: 396 mg, 60%). M.p. 158-160 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (d, J = 6 Hz, 6H), 4.83 (q, J = 7.5 Hz, 2H), 4.86 (s, 2H), 5.46 (p, J = 6 Hz, 1H), 7.72 (d, J = 9 Hz, 2H), 7.82 (s, 1H), 8.03 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 392 $(M+H)^+$. Anal. calc. for $C_{15}H_{16}F_3N_3O_4S$: C, 46.03; H, 4.12; N, 10.73. Found: C, 46.08; H, 4.22; N, 10.52.

Example 71

2-(2,2,2-Trifluoroethyl)-4-(4-fluorophenoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The methyl sulfide intermediate of Example 76 was oxidized with one equivalent of *meta*-chloroperoxybenzoic acid to provide the methylsulfoxide which was converted to the sulfonamide final product according to the method of Example 68 (yield: 180 mg, 37%). M.p. 150-152 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.71 (q, J = 7.5 Hz, 2H), 4.72 (s, 2H), 6.88 (dd, J = 9 Hz, 4.5 Hz, 2H), 7.0 (t, J = 9 Hz, 2H), 7.73 (d, J = 9 Hz, 2H), 7.98 (s, 1H), 8.05 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 444 $(M+H)^+$. Anal. calc. for $C_{18}H_{13}F_4N_3O_4S$: C, 48.76; H, 2.95; N, 9.47. Found: C, 48.49; H, 2.8; N, 8.95.

Example 72

2,4-Bis-(4-fluorophenyl)-5-[3-fluoro-4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

72A-1. 2-Fluorothioanisole

A deoxygenated solution of 2-fluorothiophenol (10 g, 78 mmol) in anhydrous DMF (10 mL) was treated with iodomethane (4.9 mL, 78 mmol) and potassium carbonate (10.8 g, 78 mmol). The reaction mixture was stirred at room temperature for 1 hour. A thin layer chromotography (100% hexanes) sample indicated that the reaction had not gone to completion, so an additional equivalent of base and iodomethane were added and the reaction mixture was stirred overnight at room temperature. The reaction was acidified with 10% aqueous citric acid and extracted with hexanes (2 X 125 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure to provide the desired compound as a pale yellow oil (yield: 6.68 g; 60%).

72A-2. 2-Fluorothioanisole

An alternative method for preparing 2-fluorothioanisole begins with a solution of 1,2-difluorobenzene (0.79 mL, 8 mmol) in anhydrous DMF (50 mL) was treated with sodium thiomethoxide (0.59 g, 8 mmol). The reaction mixture was stirred at room temperature for 6 hours, and partitioned between hexanes and water. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure to provide the desired compound (1.1 g, 100%) slightly contaminated with 1,2-bis(methylthio)benzene, a lower R_f material, which was removed by chromatography with 100% hexanes (0.9 g, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (s, 3H), 6.98-7.19 (m, 3H) 2.26 (dt, J = 9 Hz, 3 Hz, 1H).

72B. 4-Bromo-2-fluorothioanisole

A solution of 2-fluorothioanisole (1.42 g, 10 mmol) and iron powder (0.03 g, 0.5 mmol) in dichloromethane (20 mL) was chilled to °C and treated dropwise with Bromine (0.5 mL, 10 mmol). Upon completion of the Bromine treatment, the reaction was sampled for TLC (100% hexanes). A new, higher R_f material was present but the reaction had not gone to completion so another equivalent of

bromine was added along with a catalytic amount of aluminum chloride. The reaction mixture was stirred overnight at room temperature. Aqueous sodium sulfite was added to the reaction mixture and the organic layer was isolated, dried over $MgSO_4$, and filtered. The filtrate was filtered through a pad of silica gel to remove color then concentrated under reduced pressure to provide the product as a clear, colorless oil (yield: 1.3 g; 60%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.48 (s, 3H), 7.31 (t, J = 9 Hz, 1H), 7.43 (dd, J = 9 Hz, 3 Hz, 1H) 7.54 (dd, J = 9 Hz, 3 Hz, 1H).

72C. <u>3-Fluoro-4-(methylthio)benzeneboronic acid</u>

A solution of 4-bromo-2-fluorothioanisole (0.5 g, 22.6 mmol) in dry THF (20 mL) was chilled to -78 °C under a nitrogen atmosphere. The reaction mixture was treated with 1.6 M n-butyllithium in hexanes (1.7 mL, 27.1 mmol), and the mixture was warmed to -40°C where it was maintained for 0.5 hours. The reaction mixture was then chilled to -78°C and three equivalents of triisopropyl borate (1.56 mL, 67.8 mmol) were added. The reaction mixture was allowed to warm to room temperature and stirred for 1.5 hours. At this point, 10% aqueous KOH (200 mL, 360 mmol) was added and the mixture was stirred overnight at room temperature. The reaction mixture was then poured into an ice/concentrated HCl mixture with stirring to yield a white precipitate. This solid was dried in a vacuum oven (65 °C, 29 in Hg) overnight to provide the title compound (yield: 0.22 g; 52.4%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.48 (s, 3H), 7.31 (t, J = 9 Hz, 1H), 7.49 (dd, J = 12 Hz, 1.5 Hz, 1H) 7.54 (dd, J = 9 Hz, 1.5 Hz, 1H).

72D. <u>2,4-Bis-(4-fluorophenyl)-5-[3-fluoro-4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone</u>

2-Benzyl-4-chloro-5-methoxy-3(2H)-pyridazinone (*J. Het. Chem.*, **1996**, *33*, 1579-1582) was converted to the 5-hydroxy-analog according to the method of Example 7 and then to the 5-trifluoromethylsulfonyloxy-analog following the method of Example 8. Subsequent coupling to 3-fluoro-4-(methylthio)phenylboronic acid, according to the method of Example 9, provided 2-benzyl-4-chloro-5-[3-fluoro-4-(methylthio)phenyl]-3(2H)-pyridazinone. This intermediate was coupled in the 4-position with 4-fluorophenylboronic acid following the method of Example 6. This product was N-debenzylated according to the method of Example 11 and N-arylated with 4-fluoroiodobenzene according to the method of Example 62. The

resulting sulfide was oxidized with one equivalent of *meta*-chloroperoxybenzoic acid to provide the methylsulfoxide which was converted to the sulfonamide final product according to the method of Example 68 (yield: 500 mg, 75%). M.p. 222-224 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.06 (s, 2H), 7.01 (t, J = 9 Hz, 2H), 7.06 (d, J = 9 Hz, 2H), 7.10 (d, J = 9 Hz, 2H), 7.18 (t, J = 9 Hz, 2H), 7.69 (dd, J = 9 Hz, 3 Hz, 2H), 7.88 (t, J = 9 Hz, 1H), 7.95 (s, 1H). MS (DCI-NH_3) m/z 458 $(M+H)^+$. Anal. calc. for $C_{22}H_{14}F_3N_3O_3S$: C, 57.76; H, 3.08; N, 9.18. Found: C, 57.5; H, 3.15; N, 8.8.

Example 73

2-(2,2,2-Trifluoroethyl)-4-(3-fluoro-4-chlorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The methyl sulfide intermediate prepared in Example 67 was oxidized with one equivalent of *meta*-chloroperoxybenzoic acid, according to the method of Example 68 to provide the methyl sulfoxide. The methyl sulfoxide was converted to the sulfonamide product according to the method of Example 68 (yield: 1.5 g, 63%). M.p. 180-183 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.09 (q, J = 9 Hz, 2H), 7.01 (dd, J = 9 Hz, 3 Hz, 1H), 7.15 (dd, J = 9 Hz, 3 Hz, 1H), 7.39 (dd, J = 9 Hz, 3 Hz, 1H), 7.47 (dd, J = 9 Hz, 3 Hz, 1H), 7.55 (t, J = 9 Hz, 1H), 7.71 (t, J = 9 Hz, 1H), 7.78 (s, 2H), 8.37 (s, 1H). MS (DCI-NH_3) m/z 480 $(M+H)^+$. Anal. calc. for $C_{18}H_{11}ClF_5N_3O_3S$: C, 45.05; H, 2.31; N, 8.75. Found: C, 46.19; H, 3.02; N, 7.43.

Example 74

2-Benzyl-4-(2-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-Benzyl-4-chloro-5-methoxy-3(2H)-pyridazinone (*J. Het. Chem.*, **1996**, *33*, 1579-1582) was converted to the 5-hydroxy-analog according to the method of Example 7 and then to the 5-trifluoromethylsulfonyloxy-analog following the method of Example 8. Subsequent coupling to 4-(methylthio)phenylboronic acid according to the method of Example 9 provided 2-benzyl-4-chloro-5-[4-(methyl-thio)phenyl]-3(2H)-pyridazinone. This 4-chloro-intermediate thus prepared was treated with 2-propanol (20 mL, 261 mmol) and potassium *t*-butoxide (110 mg, 0.98 mmol) at reflux for 45 minutes furnished 2-benzyl-4-(2-propoxy)-5-[4-(methylthio)pentyl]-3(2H)-pyridazinone This methyl sulfide was oxidized according to the method of Example 10 to provide the title compound (yield: 180 mg, 80%). M.p. 109-111 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, J = 6 Hz, 6H), 3.12 (s, 3H), 5.36 (s, 2H), 5.49 (h, J = 6 Hz, 1H), 7.35 (m, 3H), 7.47 (dd, J = 9 Hz, 3 Hz, 2H), 7.74 (d, J = 9 Hz, 2H), 7.79 (s, 1H), 8.03 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 399

$(M+H)^+$. Anal. calc. for $C_{21}H_{22}N_2O_4S$: C, 63.29; H, 5.56; N, 7.03. Found: C, 63.17; H, 5.57; N, 6.95.

Example 75

2-Benzyl-4-(4-fluorophenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 74 substituting 4-fluorophenol in place of 2-propanol (yield: 180 mg, 99%). M.p. 188-190 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.12 (s, 3H), 5.26 (s, 2H), 6.86 (dd, J = 9 Hz, 6 Hz, 2H), 6.99 (t, J = 9 Hz, 2H), 7.34 (m, 3H), 7.46 (dd, J = 9 Hz, 3 Hz, 2H), 7.72 (d, J = 9 Hz, 2H), 7.92 (s, 1H), 8.02 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 451 $(M+H)^+$. Anal. calc. for $C_{24}H_{19}FN_2O_4S$: C, 63.98; H, 4.25; N, 6.21. Found: C, 63.74; H, 4.2; N, 6.12.

Example 76

2-(2,2,2-Trifluoroethyl)-4-(4-fluorophenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 75 substituting 2-(2,2,2-trifluoroethyl)-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-benzyl-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 180 mg, 63%). M.p. 161-164 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.09 (s, 3H), 4.81 (q, J = 9 Hz, 2H), 6.88 (dd, J = 9 Hz, 4.5 Hz, 2H), 7.0 (t, J = 9 Hz, 2H), 7.78 (d, J = 9 Hz, 2H), 7.79 (s, 1H), 8.06 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 443 $(M+H)^+$. Anal. calc. for $C_{19}H_{14}F_4N_2O_4S$: C, 51.58; H, 3.18; N, 6.33. Found: C, 51.8; H, 3.3; N, 6.22.

Example 77

2-(2,2,2-Trifluoroethyl)-4-(4-chlorophenyl)-5-[4-(methylsulfinyl)phenyl]-3(2H)-pyridazinone

2-Benzyl-4-chloro-5-methoxy-3(2H)-pyridazinone (*J. Het. Chem.*, **1996**, *33*, 1579-1582) was converted to the 5-hydroxy-analog according to the method of Example 7 and then to the 5-trifluoromethylsulfonyloxy-analog according to the method of Example 8. Subsequent coupling to 4-(methylthio)phenylboronic acid, according to the method of Example 9, provided 2-benzyl-4-chloro-5-[4-(methyl-thio)phenyl]-3(2H)-pyridazinone. This intermediate was coupled with 4-chlorophenylboronic acid according to the method of Example 6. This product was N-debenzylated according to the method of Example 11 and N-alkylated with 2-

iodo-1,1,1-trifluoroethane according to the method of Example 20. The resulting sulfide was oxidized to the corresponding sulfoxide with one equivalent of *meta*-chloroperoxybenzoic acid, according to the method of Example 5 to provide the title compound (yield: 130 mg, 70%). M.p. 154-155 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.74 (s, 3H), 4.88 (q, J = 9 Hz, 2H), 7.14 (d, J = 9 Hz, 2H), 7.26 (d, J = 9 Hz, 2H), 7.31 (d, J = 9 Hz, 2H), 7.61 (d, J = 9 Hz, 2H), 7.82 (s, 1H). MS (DCI-NH_3) m/z 427 $(M+H)^+$. Anal. calc. for $C_{19}H_{14}ClF_3N_2O_2S$: C, 53.46; H, 3.3; N, 6.56. Found: C, 53.58; H, 3.34; N, 6.42.

Example 78

2-Benzyl-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared by oxidizing 2-benzyl-4-chloro-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone, (prepared as an intermediate in Example 77) according to the method of Example 10 (yield: 180 mg, 83%). M.p. 166-167 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.12 (s, 3H), 5.41 (s, 2H), 7.37 (m, 3H), 7.53 (dd, J = 9 Hz, 3 Hz, 2H), 7.68 (d, J = 9 Hz, 2H), 7.74 (s, 1H), 8.08 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 375 $(M+H)^+$. Anal. calc. for $C_{18}H_{15}ClN_2O_3S$: C, 57.67; H, 4.03; N, 7.47. Found: C, 57.43; H, 4.06; N, 7.35.

Example 79

2-(2,2,2-Trifluoroethyl)-4-(4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-Benzyl-4-bromo-5-methoxy-3(2H)-pyridazinone (*J. Het. Chem.*, **1996**, *33*, 1579-1582) was converted to the 5-hydroxy-analog according to the method of Example 7 and then to the 5-(trifluoromethyl)sulfonyloxy-analog according to the method of Example 8. Subsequent coupling to 4-(methylthio)phenylboronic acid, according to the method of Example 9, provided 2-benzyl-4-bromo-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone. This intermediate was coupled with 4-methylphenylboronic acid according to the method of Example 6. This product was N-debenzylated according to the method of Example 11 and N-alkylated with 2-iodo-1,1,1-trifluoroethane according to the method of Example 20. The resulting sulfide was oxidized to the title compound according to the method of Example 10 (yield: 210 mg, 98%). M.p. 154-156 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H), 3.07 (s, 3H), 4.89 (q, J = 9 Hz, 2H), 7.08 (s, 4H), 7.37 (d, J = 9 Hz, 2H), 7.88 (s, 1H), 7.89 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 423 $(M+H)^+$. Anal. calc. for $C_{20}H_{17}F_3N_2O_3S$: C, 56.86; H, 4.05; N, 6.63. Found: C, 56.59; H, 4.11; N, 6.53.

Example 80

2-(2,2,2-Trifluoroethyl)-4-(4-chloro-3-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

2-Benzyl-4-chloro-5-methoxy-3(2H)-pyridazinone (*J. Het. Chem.*, **1996**, *33*, 1579-1582) was converted to the 5-hydroxy-analog according to the method of Example 7 and then to the 5-(trifluoromethyl)sulfonyloxy-analog according to the method of Example 8. Subsequent coupling to 4-(methylthio)phenylboronic acid, according to the method of Example 9, provided 2-benzyl-4-chloro-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone. This intermediate was coupled with 4-chloro-3-fluorophenylboronic acid according to the method of Example 6. This product was N-debenzylated according to the method of Example 11 and N-alkylated with 2-iodo-1,1,1-trifluoroethane according to the method of Example 20. The resulting sulfide was oxidized to the corresponding sulfoxide with one equivalent of *meta*-chloroperoxybenzoic acid to provide the methylsulfoxide which was converted to the sulfonamide final product according to the method of Example 68 (yield: 500 mg, 75%). M.p. 214-215 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.82 (s, 2H), 4.88 (q, J = 9 Hz, 2H), 6.88 (m, 1H), 7.09 (dd, J = 9 Hz, 3 Hz, 1H), 7.31 (d, J = 9 Hz, 1H), 7.32 (d, J = 9 Hz, 2H), 7.90 (s, 1H), 7.92 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 462 $(M+H)^+$. Anal. calc. for $C_{18}H_{12}F_4ClN_3O_3S$: C, 46.81; H, 2.61; N, 9.09. Found: C, 46.79; H, 2.59; N, 8.86.

Example 81

2-(2,2,2-Trifluoroethyl)-4-(3,4-dichlorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product described in Example 65 was N-debenzylated according to the method of Example 11. The intermediate was N-alkylated according to the method of Example 20, substituting 2-iodo-1,1,1-trifluoroethane in place of 4-fluorobenzyl bromide to provide the title compound (yield: 165 mg, 55%). M.p. 197-198 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.09 (s, 3H), 4.88 (q, J = 9 Hz, 2H), 6.98 (dd, J = 9 Hz, 3 Hz, 1H), 7.37 (d, J = 9 Hz, 4H), 7.91 (s, 1H), 7.95 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 477 $(M+H)^+$. Anal. calc. for $C_{19}H_{13}F_3Cl_2N_2O_3S$: C, 47.81; H, 2.74; N, 5.86. Found: C, 47.94; H, 2.87; N, 5.83.

Example 82

2-Benzyl-4-(2-propylamino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-Benzyl-4,5-dibromo-3(2H)-pyridazinone (2 g, 6 mmol) was reacted with 2-aminopropane (2 mL, 23.5 mmol) and potassium *t*-butoxide (910 mg, 6.6 mmol) in toluene (40 mL) at reflux for 18 hours to provide the 4-(2-propylamino)-derivative after column chromatography (silica gel, 92:8 hexanes/ethyl acetate). The intermediate was coupled in the 5-position with 4-(methylthio)phenylboronic acid according to the method of Example 6. The methyl sulfide was oxidized, according to the method of Example 10, to provide the title compound (yield: 120 mg, 48%). M.p. 146-147 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (d, J = 6 Hz, 6H), 3.11 (m, 1H), 3.13 (s, 3H), 5.34 (s, 2H), 5.59 (m, 1H), 7.33 (m, 3H), 7.42 (s, 1H), 7.48 (dd, J = 9 Hz, 3 Hz, 2H), 7.56 (d, J = 9 Hz, 2H), 8.00 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 399 $(M+H)^+$. Anal. calc. for $C_{21}H_{23}N_3O_3S$: C, 63.45; H, 5.83; N, 10.57. Found: C, 63.31; H, 5.87; N, 10.44.

Example 83

2-(2,2,2-Trifluoroethyl)-4-(2-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

83A. 2-(2,2,2-Trifluoroethyl)-4,5-dibromo-3(2H)-pyridazinone

A solution of mucobromic acid (10 g, 38.8 mmol) and trifluoroethyl hydrazine (70% in water, 4.88 mL, 38.8 mmol) in 100 mL of methanol was prepared and heated at reflux for 3 hours. The reaction mixture was concentrated *in vacuo* and partitioned between ethyl acetate and water. The ethyl acetate layer was dried over $MgSO_4$, filtered, passed through a silica gel pad, and concentrated *in vacuo*. The product was obtained as yellowish solid (yield: 8.8 g, 68%) . ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.78 (q, J = 9 Hz, 2H), 7.87 (s, 1H). MS (DCI-NH_3) m/z 337 $(M+H)^+$.

83B. 2-(2,2,2-Trifluoroethyl)-4-(2-propoxy)-5-bromo-3(2H)-pyridazinone

A solution of 2-(2,2,2-trifluoroethyl)-4,5-dibromo-3(2H)-pyridazinone (2 g, 6 mmol), isopropyl alcohol (3 mL) and sodium hydride (60% dispersed in oil, 290 mg, 7.2 mmol) in toluene (40 mL) was heated at reflux for 5 hours. The reaction mixture was partitioned between ethyl acetate and water. The ethyl acetate layer was filtered, and concentrated *in vacuo*. The residue was purified by chromatography (95:5 hexanes/ethyl acetate) to provide the product as a greenish oil (yield: 1.22 g,

65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (d, J = 7.5 Hz, 6H), 5.48 (h, J = 6 Hz, 1H), 7.87 (s, 1H). MS (DCI-NH_3) m/z 316 $(M+H)^+$.

83C. 2-(2,2,2-Trifluoroethyl)-4-(2-propoxy)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone

A solution of 2-(2,2,2-trifluoroethyl)-4-(2-propoxy)-5-bromo-3(2H)-pyridazinone (1.2 g, 3.8 mmol), 4-(methylthio)phenylboronic acid (704 mg, 4.19 mmol), tetrakis(triphenylphosphine)palladium(0) (220 mg, 5% mmol) and cesium carbonate (2.72 g, 8.3 mmol) in 20 mL of ethylene glycol dimethyl ether was heated to reflux for 5 hours. The mixture was partitioned between ethyl acetate and water. The ethyl acetate layer was washed with water, brine, dried over $MgSO_4$ and concentrated *in vacuo* . The residue was purified by chromatography on silica gel (94:6 hexanes/ethyl acetate). The product was obtained as a greenish solid (yield: 1.1 g, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (d, J = 7.5 Hz, 6H), 2.55 (s, 3H), 4.83 (q, J = 9 Hz, 2H), 5.28 (h, J = 6 Hz, 1H), 7.32 (d, J = 9 Hz, 2H), 7.52 (d, J = 9 Hz, 2H), 7.85 (s, 1H). MS (DCI) m/z 359 $(M+H)^+$.

83D. 2-(2,2,2-Trifluoroethyl)-4-(2-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 10, substituting 2-(2,2,2-trifluoroethyl)-4-(2-propoxy)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone in place of 4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (yield: 220 mg, 100%). M.p. 152-153 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.2 (d, J = 6 Hz, 6H), 3.13 (s, 3H), 4.84 (q, J = 9 Hz, 2H), 5.49 (p, J = 6 Hz, 1H), 7.78 (d, J = 9 Hz, 2H), 7.82 (s, 1H), 8.05 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 391 $(M+H)^+$. Anal. calc. for $C_{16}H_{17}F_3N_2O_4S$: C, 49.22; H, 4.38; N, 7.17. Found: C, 49.34; H, 4.25; N, 7.01.

Example 84

2-(2,2,2-Trifluoroethyl)-4-cyclohexyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 83, substituting cyclohexanol in place of 2-propanol (yield: 250 mg, 52%). M.p. 129-130 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.1-1.6 (m, 8H), 1.84 (m, 2H), 3.12 (s, 3H), 4.83 (q, J = 9 Hz, 2H), 5.21 (h, J = 4.5 Hz, 1H), 7.77 (s, 1H), 7.80 (d, J = 9 Hz, 2H),

8.06 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 431 $(M+H)^+$. Anal. calc. for $C_{19}H_{21}F_3N_2O_4S$: C, 53.01; H, 4.91; N, 6.50. Found: C, 52.96; H, 4.84; N, 6.45.

Example 85

2-(2,2,2-Trifluoroethyl)-4-cyclopentyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 83, substituting cyclopentanol in place of 2-propanol (yield: 250 mg, 52%). M.p. 148-150 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35-1.55 (m, 4H), 1.68-1.75 (m, 4H), 3.12 (s, 3H), 4.83 (q, J = 9 Hz, 2H), 5.89 (h, J = 4.5 Hz, 1H), 7.75 (d, J = 9 Hz, 2H), 7.83 (s, 1H), 8.04 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 417 $(M+H)^+$. Anal. calc. for $C_{18}H_{19}F_3N_2O_4S$: C, 51.91; H, 4.59; N, 6.72. Found: C, 52.04; H, 4.50; N, 6.65.

Example 86

2-(2,2,2-Trifluoroethyl)-4-(2-propylamino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

86A. 2-(2,2,2-Trifluoroethyl)-4-(2-propylamino)-5-bromo-3(2H)-pyridazinone

The title compound was prepared according method of the Example 83B, substituting 2-propylamine in place of 2-propanol (yield: 70%). MS (DCI-NH_3) m/z 315 $(M+H)^+$.

86B. 2-(2,2,2-Trifluoroethyl)-4-(2-propylamino)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone

The title compound was prepared according method of the Example 83C, substituting 2-(2,2,2-trifluoroethyl)-4-(2-propylamino)-5-bromo-3(2H)-pyridazinone in place of 2-(2,2,2-trifluoroethyl)-4-isopropoxy-5-bromo-3(2H)-pyridazinone (yield: 80%). MS (DCI-NH_3) m/z 358 $(M+H)^+$.

86C. 2-(2,2,2-Trifluoroethyl)-4-(2-propylamino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 10 , substituting 2-(2,2,2-Trifluoroethyl)-4-(2-propylamino)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone in place of 4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (yield: 180 mg, 83%). M.p. 173-174 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (d, J = 6 Hz, 6H), 3.13 (s, 3H), 4.81 (q, J = 9 Hz, 2H), 5.97 (s, 1H), 7.45 (s, 1H),

7.59 (d, J = 9 Hz, 2H), 8.03 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 340 $(M+H)^+$. Anal. calc. for $C_{16}H_{18}F_3N_3O_4S$: C, 49.35; H, 4.65; N, 10.79. Found: C, 49.29; H, 4.52; N, 10.65.

Example 87

2-Benzyl-4-(4-morpholino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-Benzyl-4,5-dichloro-3(2H)-pyridazinone, prepared following the procedure in Example 2, was reacted with morpholine following the procedure of Example 86 to provide the 4-morpholino-derivative. The morpholino intermediate was coupled at the 5-position with 4-(methylthio)phenylboronic acid according to the method of Example 6. The resulting methyl sulfide was oxidized to the title compound according to the method of Example 10 (yield: 150 mg, 69%). M.p. 158-160 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.06 (t, J = 4.5 Hz, 3H), 3.12 (s, 3H), 3.69 (t, J = 4.5 Hz, 3H), 5.33 (s, 2H), 7.35 (m, 3H), 7.5 (m, 4H), 7.58 (s, 1H), 8.05 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 426 $(M+H)^+$. Anal. calc. for $C_{22}H_{23}N_3O_4S$: C, 62.10; H, 5.44; N, 9.87. Found: C, 61.74; H, 5.47; N, 9.59.

Example 88

2-(2,3,3-Trifluoro-2-propen-1-yl)]-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

88A. 1-Methylsulfonyloxy-2,3,3-trifluoro-2-propene

2,3,3-Trifluoro-2-propen-1-ol was prepared as reported in *J. Org.Chem.*,**1989**, *54*, 5640-5642. The mesylate was obtained by reacting 2,3,3-trifluoro-2-propen-1-ol with mesyl chloride in diethyl ether. Standard workup provided the product, which was used without purification.

88B. 2-(2,3,3-Trifluoro-2-propen-1-yl)-4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone.

4-(4-Fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone is prepared starting with the 2-benzyl-pyridazinone from Example 9 and debenzylating the compound according to the procedure of Example 11.

A mixture of 4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (250 mg, 0.8 mmol), Cs_2CO_3 (650 mg, 2 mmol), and 3-methylsufonyloxy-1,1,2-trifluoropropene (mesylate, 250 mg, 1.19 mmol) in ethyl acetate (30 mL) was stirred at 55 °C for 1.5 hours. The mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried with $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by column

chromatography on silica gel eluted with 15% ethyl acetate/hexanes, to provide the methyl sulfide, 2-(2,3,3-trifluoro-2-propen-1-yl)-4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone as a greenish oil (yield: 175 mg, 53%).

88C. 2-(2,3,3-Trifluoro-2-propen-1-yl)]-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone

The methyl sulfide, prepared above, was oxidized to the title compound according to the method of Example 10 (yield: 125 mg, 68%). M.p. 154-156 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.07 (s, 3H), 5.1 (ddd, J = 21 Hz, 3 Hz, 1.5 Hz, 2H), 6.98 (t, J = 9 Hz, 2H), 7.19 (dd, J = 9 Hz, 6 Hz, 2H), 7.35 (d, J = 9 Hz, 2H), 7.89 (s, 1H), 7.9 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 439 $(M+H)^+$. Anal. calc. for $C_{20}H_{14}F_4N_2O_3S$: C, 54.79; H, 3.21; N, 6.38. Found: C, 54.52; H, 3.15; N, 6.21.

Example 89

2,4-Bis(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 68 substituting 2,4-bis(4-fluorophenyl)-5-[4-(methylsulfinyl)phenyl]-3(2H)-pyridazinone in place of 2-(2,2,2-trifluoroethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfinyl)phenyl]-3(2H)-pyridazinone (yield: 118 mg, 43%). M.p. 213-216 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.15 (t, 2H), 7.27 (m, 2H), 7.4 (m, 6H), 7.7 (dd, 2H), 7.76 (d, J = 9 Hz, 2H), 8.2 (s, 1H). MS (DCI-NH_3) m/z 440 $(M+H)^+$, 439.44 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{15}FN_2O_3S_2$: C, 60.13; H, 3.44; N, 9.56. Found: C, 59.94; H, 3.37; N, 9.46.

Example 90

2-(2,2,2-Trifluoroethyl)-4-cyclopropylmethoxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

90A. 2-(2,2,2-Trifluoroethyl)-4-methoxy-5-bromo-3(2H)-pyridazinone

The title compound was prepared according method of the Example 83B, substituting methanol in place of isopropanol (yield: 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.3 (s, 3H), 4.76 (q, J = 9 Hz, 2H), 7.85 (s, 1H). MS (DCI-NH_3) m/z 288 $(M+H)^+$.

90B. 2-(2,2,2-Trifluoroethyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone

The title compound was prepared according method of the Example 83C, substituting 2-(2,2,2-trifluoroethyl)-4-methoxy-5-bromo-3(2H)-pyridazinone in place

of 2-(2,2,2-trifluoroethyl)-4-(2-propoxy)-5-bromo-3(2H)-pyridazinone (yield: 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.54 (s, 3H), 4.11 (s, 3H), 4.82 (q, J = 9 Hz, 2H), 7.33 (d, J = 9 Hz, 2H), 7.48 (d, J = 9 Hz, 2H), 7.84 (s, 1H). MS (DCI-NH_3) m/z 331 $(M+H)^+$.

90C. <u>2-(2,2,2-Trifluoroethyl)-4-hydroxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone</u>

A solution of 2-(2,2,2-Trifluoroethyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (2 g, 6.1 mmol) and hydrobromic acid (40% in water, 20 mL) in acetic acid (40 mL) was heated at reflux for 3 hours. The reaction mixture was cooled to room temperature and water (50 mL) was added. The crystals formed were filtered, washed with water and 5% ethyl acetate in hexanes, and dried to constant weight. The product was obtained as a white solid (yield: 1.75 g, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.54 (s, 3H), 4.82 (q, J = 9 Hz, 2H), 7.47 (d, J = 9 Hz, 2H), 7.65 (d, J = 9 Hz, 2H), 7.73 (br s, 1H), 8.00 (s, 1H). MS (DCI) m/z 317 $(M+H)^+$.

90D. <u>2-(2,2,2-Trifluoroethyl)-4-cyclopropylmethoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone</u>

A solution of 2-(2,2,2-trifluoroethyl)-4-hydroxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (150 mg, 0.47 mmol), cyclopropyl methanol (43 mL, 0.52 mmol) and triphenylphosphine (124 mg, 0.47 mmol) in freshly distilled THF was prepared and added dropwise to diethyl azodicarboxylate (75 mL, 0.52 mmol) at 0 °C. The mixture was allowed to warm to room temperature, stirred for 5 hours and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (95:5 hexanes/ethyl acetate) to provide the product as a colorless oil (yield: 140 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.22 (m, 2H), 0.48 (m, 2H), 1.6 (m, 1H), 2.53 (s, 3H), 4.26 (d, J = 7.5 Hz, 2H), 4.72 (q, J = 9 Hz, 2H), 7.32 (d, J = 9 Hz, 2H), 7.55 (d, J = 9 Hz, 2H), 7.87 (s, 1H). MS (DCI-NH_3) m/z 371 $(M+H)^+$.

90E. <u>2-(2,2,2-Trifluoroethyl)-4-cyclopropylmethoxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone</u>

The title compound was prepared according to the method of example 10, substituting 2-(2,2,2-trifluoroethyl)-4-cyclopropylmethoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone in place of 4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (yield: 130 mg, 85%). M.p. 133-135 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.22 (m, 2H), 0.5 (m, 2H), 1.07 (m, 1H), 3.12 (s, 3H), 4.4 (d, J = 9 Hz, 2H), 4.83 (q, J

= 9 Hz, 2H), 7.79 (s, 1H), 7.83 (d, J = 9 Hz, 2H), 8.07 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 403 $(M+H)^+$. Anal. calc. for $C_{17}H_{17}F_3N_2O_4S$: C, 50.74; H, 4.25; N, 6.96. Found: C, 50.56; H, 4.09; N, 6.88.

Example 91

2-(2,2,2-Trifluoroethyl)-4-(3-propen-1-oxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 90, substituting 2-propen-1-ol in place of cyclopropylmethanol (yield: 120 mg, 77%). M.p. 121-123 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.12 (s, 3H), 4.84 (q, J = 12 Hz, 2H), 5.07 (d, J = 6 Hz, 2H), 5.21 (dd, J = 13.5 Hz, 1 Hz, 1H), 5.27 (dd, J = 15 Hz, 1 Hz, 1H), 5.85 (m, 1H), 7.25 (d, J = 9 Hz, 2H), 7.83 (s, 1H), 8.06 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 389 $(M+H)^+$. Anal. calc. for $C_{16}H_{15}F_3N_2O_4S$: C, 49.48; H, 3.89; N, 7.21. Found: C, 49.24; H, 3.77; N, 7.16.

Example 92

2-(2,2,2-Trifluoroethyl)-4-(4-fluoro-*alpha*-methylbenzyloxy)-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 90, substituting 4-fluoro-*alpha*-methylbenzyl alcohol in place of cyclopropylmethanol (yield: 155 mg, 76%). M.p. 133-135 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.57 (d, J = 6 Hz, 3H), 3.13 (s, 3H), 4.75 (q, J = 7.5 Hz, 1H), 4.87 (q, J = 7.5 Hz, 1H), 6.34 (q, J = 6 Hz, 1H), 6.83 (t, J = 9 Hz, 2H), 6.98 (dd, J = 9 Hz, 6 Hz, 2H), 7.59 (d, J = 9 Hz), 7.70 (s, 1H), 8.03 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 471 $(M+H)^+$. Anal. calc. for $C_{21}H_{18}F_4N_2O_4S$: C, 53.61; H, 3.85; N, 5.95. Found: C, 53.54; H, 3.73; N, 5.86.

Example 93

2-[4-(Methylthio)phenyl]-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A solution of the product from Example 11, 4-(4-Fluorophenyl)-5-[4-(methyl-sulfonyl)phenyl]-3(2H)-pyridazinone (344 mg, 1.0 mmol), 4-bromothioanisole (812 mg, 4.0 mmol), and copper (70 mg, 1.1 mmol) in 20 mL of pyridine was stirred at reflux under a nitrogen atmosphere for 18 hours. After cooling to room temperature, the reaction mixture was diluted with a mixture of water and ethyl acetate. The two layers were filtered through Celite®, and separated. The organic layer was washed with 10% aqueous citric acid, with brine, dried over $MgSO_4$, and

filtered. The filtrate was concentrated *in vacuo* and the residue purified by column chromatography (silica gel, 93:7 dichloromethane/ethyl acetate) to provide the title compound as a foam (yield: 380 mg, 81.5%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.55 (s, 3H), 3.05 (s, 3H), 6.98 (t, J = 9 Hz, 2H), 7.22 (dd, J = 9 Hz, 6 Hz, 2H), 7.38 (dd, J = 8 Hz, 2 Hz, 4H), 7.64 (d, J = 9 Hz, 2H), 7.91 (d, J = 9 Hz, 2H), 7.98 (s, 1H). MS (DCI-NH_3) m/z 467 $(M+H)^+$. Anal. calc. for $C_{24}H_{19}FN_2O_3S_2 \cdot 0.5\ H_2O$: C, 60.63; H, 4.21; N, 5.90. Found: C, 60.72; H, 3.96; N, 5.70.

Example 94

2,5-Bis[4-(methylsulfonyl)phenyl]-4-(4-fluorophenyl)-3(2H)-pyridazinone

The title compound was prepared by oxidizing the product of Example 93, according to the method of Example 10 (yield: 156 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.10 (s, 3H), 3.12 (s, 3H), 7.02 (m, 2H), 7.24 (m, 2H), 7.42 (br d, J = 9 Hz, 2H), 7.94 (dd, J = 9 Hz, 2 Hz, 2H), 8.02 (dd, J = 9 Hz, 2 Hz, 2H), 8.10 (m, 3H). MS (DCI-NH_3) m/z 499 $(M+H)^+$, 516 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{19}FN_2O_5S_2 \cdot 0.5\ H_2O$: C, 56.80; H, 3.94; N, 5.53. Found: C, 56.50; H, 3.88; N, 5.38.

Example 95

2-(3-Methyl-2-thienyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to Example 93, substituting 2-bromo-3-methylthiophene in place of 4-bromothioanisole (yield: 190 mg, 43%). M.p. 215-217 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21 (s, 3H), 3.08 (s, 3H), 6.90 (d, J = 9 Hz, 1H), 6.98 (t, J = 9 Hz, 2H), 7.24 (dd, J = 9 Hz, 6 Hz, 3H), 7.41 (d, J = 9 Hz, 2H), 7.94 (d, J = 9 Hz, 2H), 7.98 (s, 1H). MS (DCI-NH_3) m/z 441 $(M+H)^+$, 458 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{17}FN_2O_3S_2 \cdot 0.5\ H_2O$: C, 58.80; H, 4.01; N, 6. 24. Found: C, 58.85; H, 3.78; N, 5.99.

Example 96

2-(2-Trifluoromethyl-5-nitrophenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to Example 93, substituting 2-bromo-5-nitrobenzotrifluoride in place of 4-bromothioanisole (yield: 390 mg, 73%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.08 (s, 3H), 6.98 (t, J = 9 Hz, 2H), 7.21 (dd, J = 9 Hz, 6 Hz, 2H), 7.43 (d, J = 9 Hz, 2H), 7.80 (d, J = 9 Hz, 1H), 7.96 (d, J = 9 Hz, 2H), 8.02 (s, 1H), 8.61 (dd, J = 9 Hz, 3 Hz, 1H), 8.75 (d, J = 3 Hz, 1H). MS (DCI-NH_3) m/z 534

$(M+H)^+$, 551 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{15}F_4N_3O_5S{\cdot}0.75\ H_2O$: C, 52.70; H, 3.02; N, 7.69. Found: C, 52.42; H, 3.04; N, 6.82.

Example 97

2-[3-(Methylthio)phenyl]-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to Example 93, substituting 3-bromothioanisole in place of 4-bromothioanisole (yield: 355 mg, 76%). M.p. 196 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 2.55 (s, 3H), 3.08 (s, 3H), 6.99 (t, J = 9 Hz, 2H), 7.23 (dd, J = 9 Hz, 6 Hz, 2H), 7.28-7.33 (m, 1H), 7.37-7.49 (m, 2H), 7.40 (d, J = 9 Hz, 2H), 7.58 (m, 1H), 7.92 (d, J = 9 Hz, 2H), 7.99 (m, 1H). MS (DCI-NH_3) m/z 467 $(M+H)^+$, 484 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{19}FN_2O_3S_2$: C, 61.80; H, 4.08; N, 6.01. Found: C, 61.56; H, 3.93; N, 5.86.

Example 98

2-[3-(Methylsulfonyl)phenyl]-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared by oxidizing the product of Example 97, according to the method of Example 10 (yield: 98 mg, 65.6%). M.p. 141-142 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 3.25 (s, 3H), 3.35 (s, 3H), 7.18 (t, J = 9 Hz, 2H), 7.32 (dd, J = 9 Hz, 6 Hz, 2H), 7.52 (d, J = 9 Hz, 2H), 7.83 (t, J = 9 Hz, 1H), 7.95 (d, J = 9 Hz, 2H), 8.05 (m, 1H), 8.25 (t, J = 1.5 Hz, 1H), 8.33 (s, 1H). MS (DCI-NH_3) m/z 516 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{19}FN_2O_5S_2{\cdot}H_2O$: C, 55.81; H, 4.07; N, 5.43. Found: C, 56.24; H, 4.29; N, 5.10.

Example 99

2-(4-Fluorophenyl)-4-(4-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

4-(4-Chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone is prepared starting with the 2-benzylpyridazinone from Example 53 and debenzylating the compound according to the method of Example 11.

The title compound was prepared according to the method of Example 93, starting with 4-(4-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting 1-fluoro-4-iodobenzene in place of 4-bromothioanisole (yield: 245 mg, 54%). M.p. 195-197 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.08 (s, 3H), 7.19 (m, 4H),

7.25 (m, 2H), 7.41 (d, J = 9 Hz, 2H), 7.70 (m, 2H), 7.95 (d, J = 9 Hz, 2H), 8.01 (s, 1H). MS (DCI-NH_3) m/z 455 $(M+H)^+$, 472 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{16}ClFN_2O_3S$: C, 60.78; H, 3.52; N, 6.17. Found: C, 60.81; H, 3.53; N, 5.93.

Example 100

2-(5-Chloro-2-thienyl)-4-(4-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to Example 93, substituting 4-(4-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting 2-bromo-5-chlorothiophene in place of 4-bromothioanisole (yield: 150 mg, 45%). M.p. 249-251 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.05 (s, 3H), 6.92 (d, J = 9 Hz, 1H), 7.18 (d, J = 9 Hz, 2H), 7.31 (d, J = 9 Hz, 2H), 7.39 (d, J = 9 Hz, 2H), 7.58 (d, J = 6 Hz, 1H), 7.94 (d, J = 9 Hz, 2 Hz, 2H), 8.04 (s, 1H). MS (DCI-NH_3) m/z 477 $(M+H)^+$, 494 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{14}Cl_2N_2O_3S_2 \cdot H_2O$: C, 50.9; H, 3.03; N, 5.60. Found: C, 50.5; H, 2.79; N, 5.26.

Example 101

2-(3-Trifluoromethylphenyl)-4-(4-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to Example 93, starting with 4-(4-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting 3-iodobenzotrifluoride in place of 4-bromothioanisole (yield: 210 mg, 59.5%). M.p. 103-105 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.08 (s, 3H), 7.18 (d, J = 9 Hz, 2H), 7.28 (d, J = 9 Hz, 2H), 7.41 (d, J = 9 Hz, 2H), 7.65 (m, 2H), 7.95 (m, 3H), 8.04 (m, 2H). MS (DCI-NH_3) m/z 505 $(M+H)^+$, 525 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{16}ClF_3N_2O_3S$: C, 57.14; H, 3.17; N, 5.56. Found: C, 56.61; H, 3.28; N, 5.38.

Example 102

2-(3-Chloro-4-fluorophenyl)-4-(4-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to Example 93, starting with 4-(4-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (described in Example 99) in place of 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting 1-bromo-3-chloro-4-fluorobenzene in place of 4-

bromothioanisole (yield: 330 mg, 58.8%). M.p. 205 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.10 (s, 3H), 7.17 (d, J = 9 Hz, 2H), 7.23-7.31 (m, 1H), 7.28 (d, J = 9 Hz, 2H), 7.41 (d, J = 9 Hz, 2H), 7.65 (ddd, J = 9 Hz, 3 Hz, 1.5 Hz, 1H), 7.85 (dd, J = 9 Hz, 3 Hz, 1H), 7.93 (d, J = 9 Hz, 2H), 8.01 (s, 1H). MS (DCI-NH_3) m/z 489 $(M+H)^+$, 508 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{15}Cl_2N_2O_3S$: C, 56.44; H, 3.17; N, 5.73. Found: C, 56.37; H, 3.19; N, 5.64.

Example 103

2-(3-Fluorophenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to Example 93, substituting 1-fluoro-3-iodobenzene in place of 4-bromothioanisole (yield: 310 mg, 70.8%). M.p. 245-247 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.08 (s, 3H), 6.98 (t, J = 9 Hz, 2H), 7.14 (m, 1H), 7.24 (dd, J = 9 Hz, 6 Hz, 2H), 7.40 (m, 2H), 7.52 (m, 3H), 7.92 (d, J = 9 Hz, 2H), 8.01 (s, 1H). MS (DCI-NH_3) m/z 439 $(M+H)^+$, 456 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{16}F_2N_2O_3S \cdot 0.25\ H_2O$: C, 62.34; H, 3.67; N, 6.38. Found: C, 62.33; H, 3.68; N, 6.22.

Example 104

2-[2-(Methylthio)phenyl]-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to Example 93, substituting 2-bromothioanisole in place of 4-bromothioanisole (yield: 280 mg, 60%). M.p. 206-208 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 2.49 (s, 3H), 3.08 (s, 3H), 6.95 (t, J = 9 Hz, 2H), 7.25 (dd, J = 9 Hz, 6 Hz, 2H), 7.29-7.51 (m, 4H), 7.43 (d, J = 9 Hz, 2H), 7.92 (d, J = 9 Hz, 3H), 8.01 (s, 1H), 7.98 (s, 1H). MS (DCI-NH_3) m/z 467 $(M+H)^+$, 484 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{19}FN_2O_3S_2 \cdot H_2O$: C, 59.50; H, 4.13; N, 5.79. Found: C, 59.62; H, 4.15; N, 5.52.

Example 105

2-(5-Nitro-2-thienyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to Example 93, substituting 2-bromo-5-nitrothiophene in place of 4-bromothioanisole (yield: 330 mg, 70%). M.p. 252-253 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.06 (s, 3H), 7.05 (t, J = 9 Hz, 2H), 7.25 (dd, J = 9 Hz, 6 Hz, 2H), 7.40 (d, J = 9 Hz, 2H), 7.71 (d, J = 6 Hz, 1H), 7.95 (m, 3H),

8.14 (s, 1H). MS (DCI-NH_3) m/z 472 $(M+H)^+$, 489 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{14}FN_3O_5S_2 \cdot 0.5\ H_2O$: C, 52.50; H, 3.02; N, 8.75. Found: C, 52.79; H, 3.18; N, 8.74.

Example 106

2-(3,4-Difluorophenyl)-4-(4-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to Example 93, starting with 4-(4-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting 1-bromo-3,4-difluorobenzene in place of 4-bromothioanisole (yield: 310 mg, 65.7%). M.p. 187-188 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.09 (s, 3H), 7.18 (d, J = 9 Hz, 2H), 7.29 (m, 3H), 7.41 (d, J = 9 Hz, 2H), 7.52 (m, 1H), 7.65 (m, 1H), 7.92 (d, J = 9 Hz, 2H), 8.01 (s, 1H). MS (DCI-NH_3) m/z 473 $(M+H)^+$, 490 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{15}ClF_2N_2O_3S \cdot 0.5\ H_2O$: C, 57.38; H, 3.33; N, 5.82. Found: C, 57.44; H, 3.38; N, 5.52.

Example 107

2-(3-Benzothienyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to Example 93, substituting 3-bromobenzothiophene in place of 4-bromothioanisole (yield: 185 mg, 41%). M.p. 265-267 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.09 (s, 3H), 7.0 (t, J = 9 Hz, 2H), 7.27 (dd, J = 9 Hz, 6 Hz, 2H), 7.39-7.47 (m, 2H), 7.44 (d, J = 9 Hz, 2H), 7.75-7.82 (m, 1H), 7.87-7.94 (m, 2H), 7.94 (d, J = 9 Hz, 2H), 8.05 (s, 1H). MS (DCI-NH_3) m/z 477 $(M+H)^+$, 494 $(M+NH_4)^+$. Anal. calc. for $C_{25}H_{17}FN_2O_3S_2$: C, 63.03; H, 3.57; N, 5.88. Found: C, 62.89; H, 3.55; N, 5.71.

Example 108

2-(4-Fluorophenyl)-4-(4-fluorophenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

108A. 4-(4-Fluorophenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared by treating 2-benzyl-4-(4-fluorophenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 75) with $AlBr_3$ in toluene according to the procedure in Example 11 (yield: 1.8 g, 95%).

108B. 2-(4-Fluorophenyl)-4-(4-fluorophenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to Example 93, starting with 4-(4-fluorophenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting 1-fluoro-4-iodobenzene in place of 4-bromothioanisole (yield: 60 mg, 53%). M.p. 83-85 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.10 (s, 3H), 6.89-7.03 (m, 4H), 7.15 (t, J = 9 Hz, 2H), 7.65 (dd, J = 9 Hz, 6 Hz, 2H), 7.83 (d, J = 6 Hz, 2H), 8.07 (d, J = 9 Hz, 2H), 8.08 (s, 1H). MS (DCI-NH_3) m/z 455 $(M+H)^+$, 472 $(M+NH_4)^+$.

Example 109

2-(3,4-Difluorophenyl)-4-(4-fluorophenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to Example 93, substituting 1-bromo-3,4-difluorobenzene in place of 4-bromothioanisole and 4-(4-fluorophenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 108A) in place of 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 185 mg, 39%). M.p. 178-180 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.11 (s, 3H), 6.89-7.04 (m, 4H), 7.45-7.52 (m, 1H), 7.45-7.52 (m, 1H), 7.61 (dt, J = 6 Hz, 3 Hz, 1H), 7.82 (d, J = 9 Hz, 2H), 8.07 (d, J = 9 Hz, 2H), 8.08 (s, 1H). MS (DCI-NH_3) m/z 473 $(M+H)^+$, 490 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{15}F_3N_2O_4S{\cdot}0.5\,H_2O$: C, 57.38; H, 3.33; N, 5.83. Found: C, 57.17; H, 3.13; N, 5.62.

Example 110

2-(3-Bromophenyl)-4-(4-fluorophenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to Example 93, substituting 1,3-dibromobenzene in place of 4-bromothioanisole and 4-(4-fluorophenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 108A) in place of 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 260 mg, 50.5%). M.p. 208-210 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.09 (s, 3H), 6.89-7.04 (m, 4H), 7.34 (t, J = 9 Hz, 1H), 7.53 (br d, J = 9 Hz, 1H), 7.64 (br d, J = 9 Hz, 1H), 7.82 (d, J = 9 Hz, 2H), 7.87 (t, J = 1.5 Hz, 1H), 8.08 (d, J = 9 Hz, 2H), 8.09 (s, 1H). MS (DCI-NH_3) m/z 517 $(M+H)^+$, 534 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{16}BrFN_2O_4S$: C, 53.7; H, 3.11; N, 5.45. Found: C, 53.46; H, 2.88; N, 5.18.

Example 111

2-(3,5-Difluorophenyl)-4-(4-fluorophenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to Example 93, substituting 1-bromo-3,4-difluorobenzene in place of 4-bromothioanisole and 4-(4-fluorophenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 108A) in place of 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 175 mg, 37%). M.p. 209-211 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.10 (s, 3H), 6.85 (tt, J = 9 Hz, 3 Hz, 1H), 6.90-7.04 (m, 4H), 7.38 (dd, J = 9 Hz, 3 Hz, 2H), 7.81 (d, J = 9 Hz, 2H), 8.07 (d, J = 9 Hz, 2H), 8.10 (s, 1H). MS ($DCI-NH_3$) m/z 473 $(M+H)^+$, 490 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{15}F_3N_2O_4S{\cdot}H_2O$: C, 58.47; H, 3.18; N, 5.94. Found: C, 58.31; H, 3.15; N, 5.82.

Example 112

2-(3-Chlorophenyl)-4-(4-fluorophenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to Example 93, substituting 1-bromo-3-chlorobenzene in place of 4-bromothioanisole and 4-(4-fluorophenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 108A) in place of 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 25 mg, 5.3%). M.p. 211-213 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.30 (s, 3H), 7.15 (d, J = 9 Hz, 4H), 7.51-7.64 (m, 3H), 7.71-7.75 (m, 1H), 7.91 (d, J = 9 Hz, 2H), 8.06 (d, J = 9 Hz, 2H), 8.41 (s, 1H). MS ($DCI-NH_3$) m/z 471 $(M+H)^+$, 488 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{16}ClFN_2O_4S{\cdot}0.5\ H_2O$: C, 57.62; H, 3.44; N, 5.85. Found: C, 57.62; H, 3.52; N, 5.48.

Example 113

2-(4-Nitrobenzyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting 4-nitrobenzyl bromide in place of 4-fluorobenzyl bromide (yield: 164 mg, 58.9%). M.p. 183-184 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.05 (s, 3H), 5.47 (s, 2H), 6.96 (t, J = 9 Hz, 2H), 7.16 (dd, J = 9 Hz, 3 Hz, 2H), 7.32 (d, J = 9 Hz, 2H), 7.70 (d, J = 9 Hz, 2H), 7.87 (s, 1H), 7.88 (d, J = 9 Hz, 2H), 8.22 (d, J = 9 Hz, 2H). MS ($DCI-NH_3$) m/z 480 (M+H)+, m/z 497 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{18}FN_3O_5S$: C, 60.12; H, 3.78; N, 8.76. Found: C, 59.89; H, 3.83; N, 8.61.

Example 114

2-(4-Acetoxybenzyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting 4-(chloromethyl)phenyl acetate in place of 4-fluorobenzyl bromide (yield: 220 mg, 76.9%). M.p. 172-174 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3H), 3.05 (s, 3H), 5.38 (s, 2H), 6.95 (t, J = 9 Hz, 2H), 7.06 (d, J = 9 Hz, 2H), 7.16 (dd, J = 9 Hz, 5 Hz, 2H), 7.31 (d, J = 9 Hz, 2H), 7.60 (d, J = 9 Hz, 2H), 7.81 (s, 1H), 7.87 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 510 $(M+NH_4)^+$. Anal. calc. for $C_{26}H_{21}FN_2O_5S$: C, 63.40; H, 4.30; N, 5.69. Found: C, 63.28; H, 4.41; N, 5.39.

Example 115

2-(4-Hydroxybenzyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A solution of 2-(4-acetoxybenzyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone (0.2 g, 4.06 mmol) (Example 114) in THF (20 mL) was treated with a solution of lithium hydroxide monohydrate (0.05 g, 1.22 mmol) in water (5 mL). Methanol (2 mL) was added to provide a homogeneous solution which was stirred at room temperature overnight. The reaction mixture was then acidified with 10% aqueous citric acid and extracted with ethyl acetate. The ethyl acetate layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* to provide a white foam which was purified by column chromatography (silica gel, 65:35 hexanes/ethyl acetate). Product fractions were combined and concentrated *in vacuo*. The residue was crystallized from ethyl acetate/hexanes (yield: 195 mg, 70%). M.p. 225-226 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.05 (s, 3H), 4.86 (s, 1H), 5.33 (s, 2H), 6.80 (d, J = 8.5 Hz, 2H), 6.95 (t, J = 9 Hz, 2H), 7.15 (dd, J = 9 Hz, 5 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H), 7.83 (s, 1H), 7.87 (d, J = 8.5 Hz, 2H). MS (DCI-NH_3) m/z 451 $(M+H)^+$. Anal. calc. for $C_{24}H_{19}FN_2O_4S$: C, 63.99; H, 4.25; N, 6.22. Found: C, 63.73; H, 4.16; N, 6.11.

Example 116

2-(3-Nitrobenzyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting 3-nitrobenzyl bromide in place of 4-fluorobenzyl bromide (yield: 195 mg, 70%). M.p. 156-157 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.05 (s, 3H), 5.48 (s,

2H), 6.96 (t, J = 9 Hz, 2H), 7.16 (dd, J = 9 Hz, 5 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 7.54 (t, J = 7 Hz, 1H), 7.88 (s, 1H), 7.90 (d, J = 8.5 Hz, 2H), 8.19 (br d, J = 7 Hz, 1H), 8.37 (t, J = 1.7 Hz, 1H). MS (DCI-NH_3) m/z 480 (M+H)+, m/z 497 (M+NH_4)+. Anal. calc. for $C_{24}H_{18}FN_3O_5S$: C, 60.12; H, 3.78; N, 8.76. Found: C, 59.98; H, 3.73; N, 8.67.

Example 117

2-(3,4,4-Trifluoro-3-butenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting 4-bromo-1,1,2-trifluoro-1-butene in place of 4-fluorobenzyl bromide (yield: 38 mg, 14.5%). M.p. 131-132 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.92 (br d, J = 21.7 Hz, 2H), 3.06 (s, 3H), 4.47 (t, J = 6.6 Hz, 2H), 6.98 (t, J = 9 Hz, 2H), 7.17 (dd, J = 9 Hz, 5 Hz, 2H), 7.35 (d, J = 8.5 Hz, 2H), 7.85 (s, 1H), 7.89 (d, J = 8.5 Hz, 2H). MS (DCI-NH_3) m/z 453 (M+H)+, m/z 470 (M+NH_4)+. Anal. calc. for $C_{21}H_{16}F_4N_2O_3S$: C, 55.75; H, 3.56; N, 6.19. Found: C, 55.63; H, 3.62; N, 6.10.

Example 118

2-(2-Hexynyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting 1-chloro-2-hexyne in place of 4-fluorobenzyl bromide (yield: 170 mg, 69%). M.p. 79-80 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (t, J = 7.5 Hz, 3H), 1.56 (h, J = 7.5 Hz, 2H), 2.21 (m, 2H), 3.06 (s, 3H), 5.01 (t, J = 3 Hz, 2H), 6.96 (t, J = 9 Hz, 2H), 7.18 (dd, J = 9 Hz, 6 Hz, 2H), 7.34 (d, J = 9 Hz, 2H), 7.88 (s, 1H), 7.89 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 425 (M+H)$^+$. Anal. calc. for $C_{23}H_{21}FN_2O_3S$: C, 65.07; H, 4.98; N, 6.59. Found: C, 64.87; H, 4.90; N, 6.58.

Example 119

2-(3,3-Dichloro-2-propenyl)-4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting 1,1,3-trichloropropene in place of 4-fluorobenzyl bromide (yield: 1.15 g, 68%). M.p. 184-185 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.39 (d, J = 7.5 Hz, 2H), 6.43 (t, J = 7.5 Hz, 1H), 7.14 (t, J = 9 Hz, 2H), 7.23 (dd, J = 9 Hz, 6 Hz, 2H), 7.38 (d, J = 9 Hz, 2H), 7.43 (s, 2H), 7.73 (d, J = 9 Hz, 2H), 8.11 (s, 1H). MS (DCI-NH_3) m/z

454 $(M+H)^+$. Anal. calc. for $C_{19}H_{14}Cl_2F_4N_3O_3S$: C, 50.23; H, 3.1; N, 9.24. Found: C, 50.28; H, 3.29; N, 9.19.

Example 120

2-Cyclohexyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20 substituting cyclohexyl bromide in place of 4-fluorobenzyl bromide (yield: 163 mg, 76%). M.p. 169-171 °C. ^1H NMR (DMSO-d_6, 300 MHz) δ 1.23 (m, 1H), 1.41 (m, 2H), 1.71 (m, 3H), 1.87 (m, 4H), 3.23 (s, 3H), 4.85 (m, 1H), 7.11 (m, 2H), 7.22 (m, 2H), 7.46 (d, J = 9 Hz, 2H), 7.85 (d, J = 9 Hz, 2H), 8.11 (s, 1H). MS (DCI-NH_3) m/z 427 $(M+H)^+$ and m/z 444 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{23}FN_2O_3S{\cdot}0.5\ H_2O$: C, 63.43; H, 5.55; N, 6.43. Found: C, 63.25; H, 5.28; N, 6.28.

Example 121

2-Cyclopentyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting cyclopentyl bromide in place of 4-fluorobenzyl bromide (yield: 165 g, 80%). M.p. 191-193 °C. ^1H NMR (DMSO-d_6, 300 MHz) δ 1.67 (m, 2H), 1.85 (m, 4H), 2.05 (m, 2H), 3.23 (s, 3H), 5.36 (m, 1H), 7.12 (t, J = 9 Hz, 2H), 7.22 (m, 2H), 7.45 (d, J = 9 Hz, 2H), 7.85 (d, J = 9 Hz, 2H), 8.13 (s, 1H). MS (DCI-NH_3) m/z 413 $(M+H)^+$ and m/z 430 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{21}FN_2O_3S{\cdot}0.5\ H_2O$: C, 62.69; H, 5.26; N, 6.57. Found: C, 62.53; H, 4.93; N, 6.50.

Example 122

2-Cyclobutyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 20, substituting cyclobutyl bromide in place of 4-fluorobenzyl bromide (yield: 270 g, 68%). M.p. 202-203 °C. ^1H NMR (DMSO-d_6, 300 MHz) δ 1.85 (m, 2H), 2.32 (m, 2H), 2.50 (m, 2H), 5.40 (quintet, J = 7 Hz, 1H), 7.11 (t, J = 9 Hz, 2H), 7.21 (m, 2H), 7.47 (d, J = 9 Hz, 2H), 7.86 (d, J = 9 Hz, 2H), 8.16 (s, 1H). MS (DCI-NH_3) m/z 399 $(M+H)^+$ and m/z 416 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{19}FN_2O_3S{\cdot}0.75\ H_2O$: C, 61.22; H, 5.01; N, 6.80. Found: C, 61.19; H, 4.62; N, 6.73.

Example 123

2-(3-Methyl-2-butenyl)-4-(4-fluorophenyl)-5-[3-fluoro-4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

2-Benzyl-4-(4-fluorophenyl)-5-[3-fluoro-4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone prepared according to the method of Example 68 was N-debenzylated according to the method of Example 11. The intermediate was N-alkylated according to the method of Example 20, substituting 1-bromo-3-methyl-2-butene in place of 4-fluorobenzyl bromide, to provide the title compound (yield: 50 mg, 30%). M.p. 134-136 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.79 (s, 3H), 1.86 (s, 3H), 4.78 (s, 2H), 4.85 (d, J = 7.5 Hz, 2H), 5.48 (t, J = 6 Hz, 1H), 6.96 (t, J = 9 Hz, 2H), 7.18 (dd, J = 9 Hz, 6 Hz, 2H), 7.28 (d, J = 9 Hz, 2H), 7.83 (s, 1H), 7.85 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 414 $(M+H)^+$. Anal. calc. for $C_{21}H_{20}FN_3O_3S$: C, 61; H, 4.87; N, 10.16. Found: C, 60.98; H, 4.66; N, 9.95.

Example 124

2-(2,4-Difluorobenzyl)-4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 123, substituting 2,4-difluorobenzyl bromide in place of 1-bromo-3-methyl-2-butene (yield: 65 mg, 24%). M.p. 236-238 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 4.78 (s, 2H), 5.43 (s, 2H), 6.88 (m, 2H), 6.97 (t, J = 9 Hz, 2H), 7.18 (dd, J = 9 Hz, 6 Hz, 2H), 7.38 (d, J = 9 Hz, 2H), 7.55 (m, 1H), 7.85 (s, 1H), 7.86 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 472 $(M+H)^+$. Anal. calc. for $C_{23}H_{16}F_3N_3O_3S$: C, 58.59; H, 3.42; N, 8.91. Found: C, 58.44; H, 3.47; N, 8.72.

Example 125

2-(Pentafluorobenzyl)-4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 123, substituting 2,3,4,5,6-pentafluorobenzyl bromide in place of 1-bromo-3-methyl-2-butene (yield: 105 mg, 35%). M.p. 201-203 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 4.8 (s, 2H), 5.5 (s, 2H), 6.98 (t, J = 9 Hz, 2H), 7.18 (dd, J = 9 Hz, 6 Hz, 2H), 7.28 (d, J = 9 Hz, 2H), 7.32 (s, 1H), 7.37 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 526 $(M+H)^+$. Anal. calc. for $C_{23}H_{13}F_6N_3O_3S$: C, 52.57; H, 2.49; N, 7.99. Found: C, 52.66; H, 2.68; N, 7.8.

Example 126

2-(3-Cyclohexenyl)-4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 123, substituting 3-bromocyclohexene in place of 1-bromo-3-methyl-2-butene (yield: 30 mg, 10%). M.p. 206-208 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.75-1.85 (m, 3H), 2.1-2.3 (m, 3H), 4.8 (s, 2H), 5.75 (m, 2H), 6.1 (m, 1H), 6.97 (t, J = 9 Hz, 2H), 7.20 (dd, J = 9 Hz, 6 Hz, 2H), 7.28 (d, J = 9 Hz, 2H), 7.86 (d, J = 9 Hz, 2H), 7.90 (s, 1H). MS (DCI-NH_3) m/z 426 $(M+H)^+$. Anal. calc. for $C_{22}H_{20}FN_3O_3S$: C, 62.10; H, 4.73; N, 9.87. Found: C, 61.27; H, 4.75; N, 9.56.

Example 127

2-(3,4-Difluorobenzyl)-4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 123, substituting 3,4-difluorobenzyl bromide in place of 1-bromo-3-methyl-2-butene and running the reaction in DMSO instead of DMF to prevent formation of byproducts (yield: 210 mg, 62%). M.p. 253-255 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 5.33 (s, 2H), 7.13 (t, J = 9 Hz, 2H), 7.22 (dd, J = 9 Hz, 6 Hz, 2H), 7.28 (m, 1H), 7.39 (d, J = 9 Hz, 2H), 7.42 (s, 2H), 7.47 (m, 2H), 7.73 (d, J = 9 Hz, 2H), 8.12 (s, 1H). MS (DCI-NH_3) m/z 472 $(M+H)^+$. Anal. calc. for $C_{23}H_{16}F_3N_3O_3S$: C, 58.59; H, 3.42; N, 8.91. Found: C, 58.05; H, 3.55; N, 8.49.

Example 128

2-(2,3-Dihydro-1H-inden-2-yl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A solution of 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (172 mg, 0.5 mmol), prepared in Example 11, 2-indanol (67 mg, 0.5 mmol) and Ph_3P (262 mg, 1 mmol) in toluene (20 mL) and ethyl acetate (5 mL) was prepared and added dropwise a solution of DIAD (0.2 mL, 1 mmol) in toluene (10 mL). The mixture was stirred at room temperature for 6 hours and concentrated *in vacuo*. The residue was chromatographed (silica gel, 19:1 CH_2Cl_2-ethyl acetate) to provide 200 mg of product (contaminated with reduced DIAD). A second column chromatography (hexanes-ethyl acetate 1:1) furnished the title product (yield: 170 mg, 74%). M.p. 97-100 °C. ^1H NMR (DMSO-d_6, 300 MHz) δ 3.22 (s, 3H), 3.32 (m, 2H), 3.44 (dd, J = 9 Hz and 15 Hz, 2H), 5.83 (m, 1H), 7.25 (m, 4H), 7.34 (m, 4H),

7.46 (d, J = 9 Hz, 2H), 7.85 (d, J = 9 Hz, 2H), 8.06 (s, 1H). MS (DCI-NH_3) m/z 461 $(M+H)^+$ and m/z 478 $(M+NH_4)^+$.

Example 129

2-(2,3-Dihydro-1H-inden-1-yl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 128 substituting 1-indanol in place of 2-indanol (yield: 110 mg, 48%). M.p. 128-130 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.40 (m, 1H), 2.60 (m, 1H), 3.00 (m, 1H), 3.22 (s+m, 4H), 6.60 (dd, J = 9 Hz, 6 Hz, 1H), 7.16 (m, 4H), 7.27 (m, 4H), 7.47 (d, J = 9 Hz, 2H), 7.85 (d, J = 9 Hz, 2H), 8.02 (s, 1H). MS (DCI-NH_3) m/z 461 $(M+H)^+$ and m/z 478 $(M+NH_4)^+$.

Example 130

2-(4-Tetrahydro-2H-pyran-4-yl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 128 substituting 4-tetrahydropyranol in place of 2-indanol (yield: 140 g, 65%). M.p. 230-231 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.75 (m, 2H), 1.93 (m, 2H), 3.14 (s, 3H), 3.46 (m, 2H), 3.93 (m, 2H); 5.02 (m, 1H), 7.05 (t, J = 9 Hz, 2H), 7.15 (m, 2H), 7.40 (d, J = 9 Hz, 2H), 7.80 (d, J = 9 Hz, 2H), 8.08 (s, 1H). MS (APCI-) m/z 428 $(M-H)^-$ and m/z 463 $(M+Cl)^-$. Anal. calc. for $C_{22}H_{21}FN_2O_4S{\cdot}1.25\ H_2O$: C, 58.59; H, 5.25; N, 6.21. Found: C, 58.31; H, 4.75; N, 6.05.

Example 131

2-(2-Methylcyclopentyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 128 substituting 2-methylcyclopentanol in place of 2-indanol (yield: 230 g, 86%). M.p. 180-181 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.75 (d, J = 7 Hz, 3H), 1.60 (m, 2H), 1.89 (m, 2H), 2.10 (m, 1H), 2.21 (m, 1H), 2.40 (m, 1H), 3.23 (s, 3H), 5.37 (q, J = 7 Hz, 1H), 7.12 (t, J = 9 Hz, 2H), 7.21 (m, 2H), 7.47 (d, J = 9 Hz, 2H), 7.86 (d, J = 9 Hz, 2H), 8.11 (s, 1H). MS (APCI+) m/z 427 $(M+H)^+$ and (APCI-) m/z 461 $(M+Cl)^-$. Anal. calc. for $C_{23}H_{23}FN_2O_3S$: C, 64.77; H, 5.43; N, 6.56. Found: C, 64.71; H, 5.34; N, 6.28.

Example 132

2-(2-Adamantyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 128 substituting 2-adamantanol in place of 2-indanol, (yield: 75 g, 25%).M.p. 195-197 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.60 (m, 2H), 1.77 (m, 2H), 1.94 (m, 6H), 2.35 (m, 4H), 3.23 (s, 3H), 4.83 (m, 1H), 7.11 (t, J = 9 Hz, 2H), 7.22 (m, 2H), 7.47 (d, J = 9 Hz, 2H), 7.87 (d, J = 9 Hz, 2H), 8.11 (s, 1H). MS (APCI+) m/z 479 $(M+H)^+$ and (APCI-) m/z 478 $(M-H)^-$, m/z 513 $(M+Cl)^-$. Anal. calc. for $C_{27}H_{27}FN_2O_3S{\cdot}0.25\ H_2O$: C, 67.13; H, 5.73; N, 5.79. Found: C, 67.06; H, 5.76; N, 5.06.

Example 133

2-(3-Methylcyclopentyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 128 substituting 3-methylcyclopentanol in place of 2-indanol (yield: 155 g, 73%). M.p. 169-171 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.05 (dd, 2:1, 3H), 1.24 (m, 1H), 1.63 (m, 1H), 2.00 (m, 3H), 2.22 (m, 2H), 3.23 (s, 3H), 5.43 (m, 1H), 7.1 (t, J = 9 Hz, 2H), 7.21 (m, 2H), 7.46 (d, J = 9 Hz, 2H), 7.86 (d, J = 9 Hz, 2H), 8.12 (two s, 2:1, 1H). MS (APCI+) m/z 27 $(M+H)^+$ and (APCI-) m/z 426 $(M-H)^-$, m/z 461 $(M+Cl)^-$. Anal. calc. for $C_{27}H_{27}FN_2O_3S{\cdot}0.25\ H_2O$: C, 64.09; H, 5.49; N, 6.49. Found: C, 64.27; H, 5.62; N, 6.46.

Example 134

2-(1-Methylcyclopentyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A solution of 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (206 mg, 0.6 mmol), prepared according to the method of Example 11, 1-methyl-1-cyclopentanol (60 mg, 0.6 mmol), DMAP (18 mg, 0.12 mmol) and Ph_3P (262 mg, 1 mmol) in toluene (30 mL) in ethyl acetate (5 mL) was prepared and added dropwise to a solution of DIAD (0.2 mL, 1 mmol) in 10 mL of toluene. The mixture was stirred at room temperature for 6 hours and then concentrated *in vacuo*. The residue was chromatographed (silica gel, 19:1 CH_2Cl_2-ethyl acetate) to provide 80 mg of product (contaminated with reduced DIAD). A second column chromatography (hexanes-ethyl acetate 1:1) furnished the title product, (yield: 50 mg, 19%). M.p. 107-110 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.55 (s, 3H), 1.70 (m,

4H), 2.08 (m, 2H), 2.32 (m, 2H), 3.22 (s, 3H), 7.10 (t, J = 9 Hz, 2H), 7.20 (m, 2H), 7.45 (d, J = 9 Hz, 2H), 7.86 (d, J = 9 Hz, 2H), 8.03 (s, 1H). MS (APCI+) m/z 427 $(M+H)^+$ and (APCI-) m/z 426 $(M-H)^-$, m/z 461 $(M+Cl)^-$.

Example 135

2-(3,4-Difluorophenyl)-4-(4-fluoro-3-vinylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

135A. 5-Bromo-2-fluorostyrene.

A mixture of methyltriphenylphosphonium bromide (2.14 g, 6 mmol) and potassium *t*-butoxide (672 mg, 6 mmol) in 50 mL of THF was refluxed for 30 minutes under N_2 and then cooled to room temperature. 5-Bromo-2-fluorobenzaldehyde (1.02 g, 5 mmol) was added and the resulting mixture was refluxed for 2 hours (until the TLC showed the disappearance of starting aldehyde). The reaction was concentrated *in vacuo* and partitioned between water and ethyl acetate. The acetate layer was washed with water and brine. The solution was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by chromatography (silica gel, 15:1 hexanes-diethyl ether) to provide 900 mg (90%) of 5-bromo-2-fluorostyrene.

135B. 2-(3,4-Difluorophenyl)-4-(4-fluoro-3-vinylphenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone.

The bromo-styrene compound, prepared above, in 10 mL of THF was added dropwise to a heated mixture of magnesium turnings (120 mg, 5 mmol) and a few drops of 1,2-dibromoethane in THF (20 mL) at a rate to maintain a gentle reflux. The mixture was refluxed for the next 30 minutes and cooled to room temperature. The Grignard reagent solution was cooled to -78 °C and added, dropwise, to a solution of 2-(3,4-difluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (540 mg, 1.5 mmol) in THF (20 mL). The reaction mixture was allowed to warm to room temperature for 12 hours. Afterwards, a saturated solution of NH_4Cl was added and the mixture was extracted with ethyl acetate to provide 320 mg of crude sulfide.

135C. 2-(3,4-Difluorophenyl)-4-(4-fluoro-3-vinylphenyl)-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone.

The sulfide, prepared above, was dissolved in CH_2Cl_2 (20 mL) and at 0 °C was treated with 30% CH_3CO_3H in CH_3CO_2H (0.5 mL). After 1.5 hours, 10% $NaHCO_3$ was added and the mixture extracted with CH_2Cl_2. The extract was concentrated *in vacuo* and the residue purified by chromatography (silica gel, 1:1

hexanes-ethyl acetate) to provide the title compound (yield: 270 mg, 37%). ^1H NMR (DMSO-d_6, 300 MHz) δ 3.22 (s, 3H), 5.37 (d, J = 12 Hz, 1H), 5.65 (d, J = 18 Hz, 1H), 6.77 (dd, J = 12 Hz and 18 Hz, 1H), 7.15 (m, 2H), 7.57 (m, 5H), 7.90 (m, 3H), 8.28 (s, 1H). MS (APCI+) m/z 483 $(M+H)^+$ and (APCI-) m/z 517 $(M+Cl)^-$. Anal. calc. for $C_{25}H_{17}F_3N_2O_3S{\cdot}0.5\ H_2O$: C, 61.09; H, 3.69; N, 5.69. Found: C, 61.04; H, 3.71; N, 5.34.

Example 136

2-(3,4-Difluorophenyl)-4-(6-methyl-3-heptenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A Grignard, prepared as described in Example 135, substituting 2-(2-bromoethyl)-1,3-dioxane (586 mg, 3 mmol) in place of 5-bromo-2-fluorostyrene, was added to a solution of 2-(3,4-difluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (720 mg, 2 mmol) in THF (30 mL) at -78 °C. The mixture was left at room temperature for 14 hours, quenched with a saturated solution of NH_4Cl and extracted with ethyl acetate to obtain 900 mg of crude sulfide.

The intermediate sulfide product was dissolved in CH_2Cl_2 (10 mL) and treated at 0 °C with 33% solution of CH_3CO_3H in CH_3CO_2H (0.7 mL) for 1 hour. The mixture was concentrated *in vacuo* and the residue was partitioned between saturated $NaHCO_3$ and ethyl acetate. The acetate layer was dried over $MgSO_4$ and concentrated *in vacuo* to provide 950 mg of crude sulfonyl derivative.

The sulfonyl compound, prepared above, was dissolved in acetone (50 mL) and treated with 2 N HCl (10 mL). The resulting mixture was refluxed for 16 hours and concentrated *in vacuo*. The residue was extracted with ethyl acetate to provide 900 mg of 2-(3,4-difluorophenyl)-4-(2-formylethyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (crude aldehyde, contaminated with some unreacted starting dioxane derivative).

A mixture of isoamyltriphenylphosphonium bromide (414 mg, 1 mmol) and potassium *t*-butoxide (112 mg, 1 mmol) in toluene (25 mL) was refluxed for 30 minutes and then cooled to room temperature. The crude aldehyde was added and the mixture was refluxed for 14 hours. The reaction mixture was then cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in ethyl acetate and was washed with water, 10% citric acid, brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (silica gel, 1:1 hexanes-ethyl acetate) provided the title compound as an oil (yield: 120 mg, 13%). ^1H NMR (300 MHz, DMSO-d_6) δ 0.74 (d, J = 7 Hz, 6H), 1.44 (m, 1H), 1.70 (t, J = 7

Hz, 2H), 2.22 (m, 2H), 2.54 (m, 2H); 3.30 (s, 3H), 5.29 (m, 2H), 7.51 (m, 1H), 7.63 (m, 1H), 7.74 (d, J = 9 Hz, 2H), 7.82 (m, 1H), 8.02 (s, 1H), 8.10 (d, J = 9 Hz, 2H). MS (APCI+) m/z 473 $(M+H)^+$ and (APCI-) m/z 471 $(M-H)^-$, m/z 507 $(M+Cl)^-$. Anal. calc. for $C_{25}H_{26}F_2N_2O_3S$: C, 63.54; H, 5.54; N, 5.92. Found: C, 63.74; H, 5.67; N, 5.58.

Example 137

2-(3,4-Difluorophenyl)-4-(3-cyclopropylidenepropyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 136 substituting cyclopropyltriphenylphosphonium bromide in place of isoamyltriphenylphosphonium bromide (yield: 55 mg, 12%). M.p. 128-129 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 0.81 (m, 2H), 0.97 (m, 2H), 2.34 (m, 2H), 2.65 (m, 2H), 3.32 (s, 3H), 5.64 (m, 1H), 7.52 (m, 1H), 7.63 (m, 1H), 7.73 (d, J = 9 Hz, 2H), 7.81 (m, 1H), 8.02 (s, 1H), 8.10 (d, J = 9 Hz, 2H). MS (APCI+) m/z 443 $(M+H)^+$ and (APCI-) m/z 441 $(M-H)^-$, m/z 477 $(M+Cl)^-$. Anal. calc. for $C_{23}H_{20}F_2N_2O_3S \cdot 0.5\ H_2O$: C, 61.18; H, 4.68; N, 6.20. Found: C, 61.48; H, 4.60; N, 6.02.

Example 138

2-(3,4-Difluorophenyl)-4-(5-methyl-3-hexenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound, an oil, was prepared according to the method of Example 136 substituting isobutyltriphenylphosphonium bromide in place of isoamyltriphenylphosphonium bromide (yield: 170 mg, 74%). ^1H NMR (300 MHz, DMSO-d_6) δ 0.75 (d, J = 7 Hz, 6H), 2.22 (m, 3H), 2.54 (m, 2H), 3.32 (s, 3H), 5.12 (m, 2H), 7.52 (m, 1H), 7.60 (m, 1H), 7.72 (d, J = 9 Hz, 2H), 7.80 (m, 1H), 8.02 (s, 1H), 8.10 (d, J = 9 Hz, 2H). MS (APCI+) m/z 459 $(M+H)^+$ and (APCI-) m/z 457 $(M-H)^-$, m/z 493 $(M+Cl)^-$. Anal. calc. for $C_{24}H_{24}F_2N_2O_3S$: C, 62.86; H, 5.27; N, 6.10. Found: C, 62.57; H, 5.32; N, 5.81.

Example 139

2-(3,4-Difluorophenyl)-4-(5-methylhexyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound, an oil, was prepared according to the method of Example 135B, substituting 5-methylhexylmagnesium bromide for 3-fluoro-4-vinylphenylmagnesium bromide, (yield: 28 mg, 10%). ^1H NMR (300 MHz, DMSO-d_6) δ 0.77 (d, J = 7 Hz, 6H), 0.88 (m, 1H), 1.03 (m, 2H), 1.20 (m, 1H), 1.46 (m, 5H),

3.32 (s, 3H), 7.52 (m, 1H), 7.62 (m, 1H), 7.75 (d, J = 9 Hz, 2H), 7.82 (m, 1H), 8.02 (s, 1H), 8.11 (d, J = 9 Hz, 2H). MS (APCI+) m/z 461 $(M+H)^+$ and (APCI-) m/z 459 $(M-H)^-$, m/z 495 $(M+Cl)^-$.

Example 140

2-(3-Chloro-1-methyl-2E-propenyl)-4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 127, substituting 1,3-dichloro-1-butene in place of 3,4-difluorobenzyl bromide (yield: 55 mg, 30%). M.p. 152-154 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 4.71 (dt, J = 15 Hz, 7.5 Hz, 2H), 2.28 (d, J = 1.5 Hz, 3H), 4.8 (s, 2H), 4.99 (d, J = 1 Hz, 1H), 5.02 (d, J = 1 Hz, 1H), 5.85 (td, J = 4 Hz, 1 Hz, 1H), 6.98 (t, J = 9 Hz, 2H), 7.19 (dd, J = 9 Hz, 6 Hz, 2H), 7.28 (d, J = 9 Hz, 2H), 7.86 (s, 1H), 7.87 (d, J = 9 Hz, 2H). MS ($DCI-NH_3$) m/z 434 $(M+H)^+$. Anal. calc. for $C_{20}H_{17}ClFN_3O_3S$: C, 55.36; H, 3.94; N, 9.68. Found: C, 54.99; H, 3.83; N, 9.34.

Example 141

2-(2,3,3-Trifluoro-2-propen-1-yl)-4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 127, substituting 1-methylsufonyloxy-2,2,3-trifluoro-1-propene (mesylate), prepared in Example 88, in place of 3,4-difluorobenzyl bromide (yield: 10 mg, 4%). M.p. 173-175 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 4.39 (s, 2H), 5.09 (ddd, J = 26 Hz, J = 3 Hz, J = 1 Hz, 2H), 6.98 (t, J = 9 Hz, 2H), 7.19 (dd, J = 9 Hz, J = 6 Hz, 2H), 7.29 (d, J = 9 Hz, 2H), 7.78 (s, 1H), 7.78 (d, J = 9 Hz, 2H). MS ($DCI-NH_3$) m/z 440 $(M+H)^+$, MS (FAB, high res.) m/z calc. for $C_{19}H_{14}F_4N_3O_3S$: 440.0692 $(M+H)^+$. Found: 440.0695 $(M+H)^+$, (0.7 ppm error).

Example 142

2-(1,1,2-Trifluoro-2-propenyl)-4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was isolated from the same reaction mixture (Example 141) that was used to prepare 2-(2,3,3-trifluoro-2-propen-1-yl)-4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone (The title product is a result of an S_N2' attack.) (yield: 50 mg, 20%). M.p. 230-232 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 4.7 (s, 2H), 5.28 (dd, J = 15 Hz, 4.5 Hz, 1H), 5.39 (dd, J = 45 Hz, 4.5 Hz, 1H), 6.98 (t,

J = 9 Hz, 2H), 7.19 (dd, J = 9 Hz, 6 Hz, 2H), 7.31 (d, J = 9 Hz, 2H), 7.9 (d, J = 9 Hz, 2H), 7.92 (s, 1H), . MS (DCI-NH_3) m/z 440 $(M+H)^+$. Anal. calc. for $C_{19}H_{13}F_4N_3O_3S$: C, 51.93; H, 2.98; N, 9.56. Found: C, 51.88; H, 3.01; N, 9.15.

Example 143

2-(3,3-Difluoro-2-propenyl)-4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 127, substituting 1,3-dibromo-1,1-difluoropropane in place of 3,4-difluorobenzyl bromide and employing 5 equivalents of potassium carbonate (yield: 220 mg, 65%). M.p. 191-194 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 4.77 (d, J = 7.5 Hz, 2H), 4.95 (dtd, J = 24 Hz, 7.5 Hz, 1 Hz, 1H), 7.12 (t, J = 9 Hz, 2H), 7.23 (dd, J = 9 Hz, 6 Hz, 2H), 7.49 (d, J = 9 Hz, 2H), 7.50 (s, 2H), 7.74 (d, J = 9 Hz, 2H), 8.1 (s, 1H). MS (DCI-NH_3) m/z 422 $(M+H)^+$. Anal. calc. for $C_{19}H_{14}F_3N_3O_3S$: C, 54.15; H, 3.34; N, 9.97. Found: C, 53.88; H, 3.42; N, 9.76.

Example 144

2-(α–Methyl-3-fluorobenzyl)-4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 127, substituting 3-fluoro-α–methylbenzyl chloride in place of 3,4-difluorobenzyl bromide (yield: 220 mg, 65%). M.p. 192-194 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 1.76 (d, 6 Hz, 3H), 6.27 (q, J = 7 Hz, 1H), 7.1 (t, J = 9 Hz, 2H), 7.22 (dd, J = 9 Hz, 6 Hz, 2H), 7.49 (d, J = 9 Hz, 2H), 7.51 (s, 2H), 7.72 (d, J = 9 Hz, 2H), 8.18 (s, 1H). MS (DCI-NH_3) m/z 468 $(M+H)^+$. Anal. calc. for $C_{24}H_{19}F_2N_3O_3S$: C, 61.66; H, 4.09; N, 8.98. Found: C, 61.36; H, 3.96; N, 8.86.

Example 145

2-(1-Cyclohexenylmethyl)-4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 127, substituting 1-bromomethylcyclohexene in place of 3,4-difluorobenzyl bromide (yield: 70 mg, 28%). M.p. 192-193 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 1.55 (m, 4H), 1.98 (m, 4H), 4.64 (s, 2H), 5.53 (s, 1H), 7.12 (t, J = 9 Hz, 2H), 7.22 (dd, J = 9 Hz, 6 Hz, 2H), 7.39 (d, J = 9 Hz, 2H), 7.39 (s, 2H), 7.72 (d, J = 9 Hz, 2H), 8.07 (s, 1H).

MS (DCI-NH_3) m/z 440 $(M+H)^+$. Anal. calc. for $C_{23}H_{22}FN_3O_3S$: C, 62.85; H, 5.04; N, 9.56. Found: C, 62.47; H, 5.23; N, 9.14.

Example 146

2-(α–Methyl-2,3,4-trifluorobenzyl)-4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 127, substituting 2,3,4-trifluoro-α–methylbenzyl chloride in place of 3,4-difluorobenzyl bromide (yield: 70 mg, 50%). M.p. 192-194 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84 (d, J = 6 Hz, 3H), 4.8 (s, 2H), 6.54 (q, J = 7 Hz, 1H), 6.96 (t, J = 9 Hz, 2H), 6.99 (m, 1H), 7.18 (dd, J = 9 Hz, 6 Hz, 2H), 7.2 (m, 1H), 7.38 (d, J = 9 Hz, 2H), 7.86 (d, J = 9 Hz, 2H), 7.88 (s, 1H). MS (DCI-NH_3) m/z 504 $(M+H)^+$. Anal. calc. for $C_{24}H_{17}F_4N_3O_3S$: C, 57.25; H, 3.4; N, 8.34. Found: C, 56.84; H, 3.52; N, 7.91.

Example 147

2-(α–Methyl-3,5-difluorobenzyl)-4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 127, substituting 3,5-difluoro-α–methylbenzyl chloride in place of 3,4-difluorobenzyl bromide (yield: 80 mg, 45%). M.p. 139-141 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83 (d, J = 6 Hz, 3H), 4.79 (s, 2H), 6.32 (q, J = 7 Hz, 1H), 6.84 (m, 1H), 6.97 (t, J = 9 Hz, 2H), 7.02 (dd, J = 6 Hz, 1.5 Hz, 2H), 7.18 (dd, J = 9 Hz, 6 Hz, 2H), 7.28 (d, J = 9 Hz, 2H), 7.85 (s, 1H), 7.9 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 486 $(M+H)^+$. Anal. calc. for $C_{24}H_{18}F_3N_3O_3S$: C, 59.37; H, 3.73; N, 8.65. Found: C, 59.00; H, 3.70; N, 8.35.

Example 148

2-(α–Methyl-3,4-difluorobenzyl)-4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 127, substituting 3,4-difluoro-α–methylbenzyl chloride in place of 3,4-difluorobenzyl bromide (yield: 200 mg, 58%). M.p. 214-215 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.82 (d, J = 6 Hz, 3H), 4.7 (s, 2H), 6.35 (q, J = 7 Hz, 1H), 6.96 (t, J = 9 Hz, 2H), 7.16 (m, 4H), 7.28 (d, J = 9 Hz, 2H), 7.37 (m, 1H), 7.84 (d, J = 9 Hz, 2H), 7.90 (s, 1H). MS (DCI-NH_3) m/z 486 $(M+H)^+$. Anal. calc. for $C_{24}H_{18}F_3N_3O_3S$: C, 59.37; H, 3.73; N, 8.65. Found: C, 59.13; H, 3.73; N, 8.54.

Example 149

2-(3-Fluorobenzyl)-4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 127, substituting 3-fluorobenzyl bromide in place of 3,4-difluorobenzyl bromide (yield: 160 mg, 61%). M.p. 220-222 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.37 (s, 2H), 7.12 (t, J = 9 Hz, 2H), 7.22 (m, 5H), 7.39 (m, 5H), 7.73 (d, J = 9 Hz, 2H), 8.11 (s, 1H). MS (DCI-NH_3) m/z 454 $(M+H)^+$. Anal. calc. for $C_{23}H_{17}F_2N_3O_3S$: C, 60.92; H, 3.77; N, 9.26. Found: C, 61.06; H, 4.22; N, 8.88.

Example 150

2-(4-Fluorobenzyl)-4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 127, substituting 4-fluorobenzyl bromide in place of 3,4-difluorobenzyl bromide (yield: 85 mg, 34%). M.p. 237-239 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.32 (s, 2H), 7.12 (t, J = 9 Hz, 2H), 7.22 (m, 4H), 7.38 (m, 4H), 7.47 (dd, J = 9 Hz, 6 Hz, 2H), 7.72 (d, J = 9 Hz, 2H), 8.10 (s, 1H). MS (DCI-NH_3) m/z 454 $(M+H)^+$. Anal. calc. for $C_{23}H_{17}F_2N_3O_3S$: C, 60.92; H, 3.77; N, 9.26. Found: C, 60.61; H, 3.96; N, 8.74.

Example 151

2-(2,4,6-Trifluorobenzyl)-4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 127, substituting 2,4,6-trifluorobenzyl bromide in place of 3,4-difluorobenzyl bromide (yield: 255 mg, 73%). M.p. 201-203 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.38 (s, 2H), 7.13 (t, J = 9 Hz, 2H), 7.23 (m, 4H), 7.38 (d, J = 9 Hz, 2H), 7.42 (s, 2H), 7.70 (d, J = 9 Hz, 2H), 8.08 (s, 1H). MS (DCI-NH_3) m/z 490 $(M+H)^+$. Anal. calc. for $C_{23}H_{15}F_4N_3O_3S$: C, 56.44; H, 3.08; N, 8.58. Found: C, 56.31; H, 3.09; N, 8.40.

Example 152

2-(2,4,5-Trifluorobenzyl)-4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 127, substituting 2,4,5-trifluorobenzyl bromide in place of 3,4-difluorobenzyl bromide (yield: 180 mg, 49%). M.p. 236-238 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.35 (s,

2H), 7.13 (t, J = 9 Hz, 2H), 7.23 (dd, J = 9 Hz, 6 Hz, 2H), 7.39 (d, J = 9 Hz, 2H), 7.41 (s, 2H), 7.6 (m, 2H), 7.72 (d, J = 9 Hz, 2H), 8.11 (s, 1H). MS (DCI-NH_3) m/z 490 $(M+H)^+$. Anal. calc. for $C_{23}H_{15}F_4N_3O_3S$: C, 56.44; H, 3.08; N, 8.58. Found: C, 56.38; H, 3.28; N, 8.41.

Example 153

2-(2,3,4-Trifluorobenzyl)-4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 127, substituting 2,3,4-trifluorobenzyl bromide in place of 3,4-difluorobenzyl bromide (yield: 220 mg, 63%). M.p. 218-220 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 5.40 (s, 2H), 7.13 (t, J = 9 Hz, 2H), 7.22 (dd, J = 9 Hz, 6 Hz, 2H), 7.34 (m, 2H), 7.39 (d, J = 9 Hz, 2H), 7.42 (s, 2H), 7.73 (d, J = 9 Hz, 2H), 8.12 (s, 1H). MS (DCI-NH_3) m/z 490 $(M+H)^+$. Anal. calc. for $C_{23}H_{15}F_4N_3O_3S$: C, 56.44; H, 3.08; N, 8.58. Found: C, 56.32; H, 3.24; N, 8.31.

Example 154

2-(4,4,4-Trifluoro-3-methyl-2E-butenyl)-4-(4-fluorophenyl)-5-[4-(aminosulfonyl)-phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 123, substituting 1-bromo-3-methyl-4,4,4-trifluoro-2-butene in place of 1-bromo-3-methyl-2-butene (yield: 160 mg, 48%). M.p. 155-157 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 2.00 (s, 3H), 4.8 (s, 2H), 4.96 (d, J = 7.5 Hz, 2H), 6.33 (m, 1H), 6.99 (t, J = 9 Hz, 2H), 7.19 (dd, J = 9 Hz, 6 Hz, 2H), 7.29 (d, J = 9 Hz, 2H), 7.95 (s, 1H), 7.97 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 468 $(M+H)^+$. Anal. calc. for $C_{21}H_{17}F_4N_3O_3S$: C, 53.96; H, 3.66; N, 8.98. Found: C, 53.84; H, 3.51; N, 8.77.

Example 155

2-(4-Biphenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62 substituting 4-bromobiphenyl in place of 4-iodo-1-fluorobenzene (yield: 0.275 g, 100%). M.p. 249-251 °C. ^1H NMR (300 MHz, DMSO d_6) δ 3.24 (s, 3H), 7.16 (m, 2H), 7.30 (m, 2H), 7.42 (m, 1H), 7.48-7.58 (m, 4H), 7.75 (m, 4H), 7.84 (m, 2H), 7.91 (m, 2H), 8.27 (s, 1H). MS (DCI-NH_3) m/z 497 $(M+H)^+$, 514 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{21}FN_2O_3S$: C, 70.15; H, 4.26; N, 5.64. Found: C, 69.81; H, 4.42; N, 5.41.

Example 156

2-(4-Bromophenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62 substituting 1,4-dibromobenzene in place of 4-iodo-1-fluorobenzene (yield: 0.337 g, 93%). ^{1}H NMR (300 MHz, DMSO d_6) δ 3.24 (s, 3H), 7.14 (m, 2H), 7.28 (m, 2H), 7.64 (m, 2H), 7.75 (m, 2H), 7.90 (m, 2H), 8.25 (s, 1H). MS (DCI-NH_3) m/z 499 $(M+H)^+$, 518 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{16}BrFN_2O_3S{\cdot}0.75\ H_2O$: C, 53.86; H, 3.43; N, 5.46. Found: C, 53.92; H, 3.16; N, 5.34.

Example 157

2-(4-Nitrophenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62 substituting 1-iodo-4-nitrobenzene in place of 4-iodo-1-fluorobenzene (yield: 0.45 g, 100%). M.p. 110-116 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 3.24 (s, 3H), 7.17 (m, 2H), 7.32 (m, 2H), 7.53 (m, 2H), 7.91 (m, 2H), 8.03 (m, 2H), 8.34 (s, 1H), 8.40 (m, 2H). MS (DCI-NH_3) m/z 466 $(M+H)^+$, 483 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{16}FN_3O_5S$: C, 59.35; H, 3.46; N, 9.03. Found: C, 59.02; H, 3.62; N, 8.82.

Example 158

2-(4-Phenoxyphenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62 substituting 4-bromodiphenylether in place of 4-iodo-1-fluorobenzene (yield: 0.667 g, 22%). M.p. 118-125 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 3.24 (s, 3H), 7.12 (m, 5H), 7.15-7.33 (m, 4H), 7.46 (m, 2H), 7.52 (m, 2H), 765 (m, 2H), 7.90 (m, 2H), 8.23 (s, 1H). MS (DCI-NH_3) m/z 513 $(M+H)^+$. Anal. calc. for $C_{25}H_{21}FN_2O_4S{\cdot}0.75\ H_2O$: C, 66.21; H, 4.31; N, 5.32. Found: C, 65.98; H, 4.25; N, 5.27.

Example 159

2-(4-*t*-Butylphenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62 substituting 1-bromo-4-*t*-butyl-benzene in place of 4-iodo-1-fluorobenzene. No product was observed. The solution was concentrated *in vacuo*. The resulting

solid was dissolved in DMF (5 mL) and CuI (13.3 mg, 0.07 mmol) was added. The solution was allowed to reflux overnight. Upon completion, the mixture was poured into 10% citric acid and extracted with ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The crude solid was purified using flash chromatography (SiO_2), eluting with 5% diethyl ether/CH_2Cl_2 to provide the desired product (yield: 0.292 g, 84%). M.p. 132-136 °C. ^1H NMR (300 MHz, DMSO d_6) δ 1.34 (s, 9H), 3.24 (s, 3H), 7.14 (m, 2H), 7.29 (m, 2H), 7.54 (m, 6H), 7.90 (m, 2H), 8.23 (s, 1H). MS (DCI-NH_3) m/z 477 $(M+H)^+$, 494 $(M+NH_4)^+$. Anal. calc. for $C_{27}H_{25}FN_2O_3S$: C, 68.05; H, 5.29; N, 5.88. Found: C, 67.94; H, 5.31; N, 5.67.

Example 160

2-(4-Chlorophenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62 substituting 4-bromo-1-chlorobenzene in place of 4-iodo-1-fluorobenzene (yield: 0.254 g, 83.5%). M.p. 214-216 °C. ^1H NMR (300 MHz, DMSO d_6) δ 3.24 (s, 3H), 7.16 (m, 2H), 7.29 (m, 2H), 7.52 (m, 2H), 7.61 (m, 2H), 7.71 (m, 2H), 7.91 (m, 2H), 8.26 (s, 1H). MS (DCI-NH_3) m/z 455 $(M+H)^+$, 472 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{16}ClFN_2O_3S$: C, 60.73; H, 3.55; N, 6.16. Found: C, 60.45, H, 3.41; N, 6.05.

Example 161

2-(3-Methylphenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62 substituting 3-bromotoluene in place of 4-iodo-1-fluorobenzene (yield: 0.262 g, 83%). M.p. 213-216 °C. ^1H NMR (300 MHz, DMSO d_6) δ 2.39 (s, 3H), 3.24 (s, 3H), 7.14 (m, 2H), 7.28 (m, 3H), 7.43 (m, 3H), 7.53 (m, 2H), 7.80 (m, 2H), 8.22 (s, 1H). MS (DCI-NH_3) m/z 435 $(M+H)^+$, 452 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{19}FN_2O_3S$: C, 66.35; H, 4.41; N, 6.45. Found: C, 66.00, H, 4.16; N, 6.23.

Example 162

2-(3-Vinylphenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62 substituting 3-bromostyrene in place of 4-iodo-1-fluorobenzene (yield: 0.202 g,

62%). M.p. 182-183 °C. ^1H NMR (300 MHz, DMSO d_6) δ 3.25 (s, 3H), 5.35 (d, J = 12 Hz, 1H), 5.92 (d, J = 15 Hz, 1H), 6.82 (m, 1H), 7.15 (m, 2H), 7.30 (m, 2H), 7.50-7.60 (m, 4H), 7.74 (m, 1H), 7.91 (m, 2H), 8.24 (s, 1H). MS (DCI-NH_3) m/z 447 $(M+H)^+$, 464 $(M+NH_4)^+$. Anal. calc. for $C_{25}H_{19}FN_2O_3S{\cdot}0.50\ H_2O$: C, 65.92; H, 4.42; N, 6.14. Found: C, 65.86; H, 4.40; N, 6.07.

Example 163

2-(2-Formylphenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title was prepared according to the method of Example 62 substituting 2-bromobenzaldehyde in place of 4-iodo-1-fluorobenzene (yield: 0.196 g, 60%). M.p. 234-236 °C. ^1H NMR (300 MHz, DMSO d_6) δ 3.24 (s, 3H), 7.15 (m, 2H), 7.27 (m, 2H), 7.54 (m, 2H), 7.64-7.75 (m, 2H), 7.86-7.95 (m, 3H), 8.01 (m, 1H), 8.29 (s, 1H), 10.02 (s, 1H). MS (DCI-NH_3) m/z 449 $(M+H)^+$. Anal. calc. for $C_{24}H_{17}FN_2O_4S{\cdot}0.50\ H_2O$: C, 63.01; H, 3.96; N, 6.12. Found: 63.04; H, 3.82; N, 5.88.

Example 164

2-(2-Nitrophenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62 substituting 1-bromo-2-nitrobenzene in place of 4-iodo-1-fluorobenzene (yield: 0.307 g, 90.8%). M.p. 236-239 °C. ^1H NMR (300 MHz, DMSO d_6) δ 3.24 (s, 3H), 7.12-7.27 (m, 4H), 7.56 (m, 2H), 7.7-8.01 (m, 5H), 8.18 (m, 1H), 8.35 (s, 1H). MS (DCI-NH_3) m/z 466 $(M+H)^+$, 483 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{16}FN_3O_5S{\cdot}0.25\ H_2O$: C, 58.78; H, 3.53; N, 8.94. Found: C, 58.63; H, 3.54; N, 8.88.

Example 165

2-(3-Chlorophenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62 substituting 1-bromo-3-chlorobenzene in place of 4-iodo-1-fluorobenzene (yield: 0.255 g, 77%). M.p. 232-235 °C. ^1H NMR (300 MHz, DMSO d_6) δ 3.23 (s, 3H), 7.14 (m, 2H), 7.29 (m, 2H), 7.49-7.58 (m, 4H), 7.66 (m, 1H), 7.79 (m, 1H), 7.90 (m, 2H), 8.25 (s, 1H). MS (DCI-NH_3) m/z 455 $(M+H)^+$, 472 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{16}ClFN_2O_3S$: C, 60.73; H, 3.55; N, 6.16. Found: C, 60.40; H, 3.43; N, 5.98.

Example 166

2-(3-Bromophenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62 substituting 1,3 dibromobenzene in place of 4-iodo-1-fluorobenzene (yield: 0.216 g, 60%). M.p. 210-212 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 3.23 (s, 3H), 7.15 (m, 2H), 7.29 (m, 2H), 7.48-7.55 (m, 3H), 7.69 (m, 2H), 7.90 (m, 3H), 8.26 (s, 1H). MS (DCI-NH_3) m/z 499 $(M+H)^+$, 519 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{16}BrFN_2O_3S$: C, 55.32; H, 3.23; N, 5.61. Found: C, 55.12; H, 3.12; N, 5.51.

Example 167

2-(4-Cyanophenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62 substituting 4-bromobenzonitrile in place of 4-iodo-1-fluorobenzene (yield: 0.349 g, 100%). M.p. 273-278 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 3.24 (s, 3H), 7.11-7.21 (m, 2H), 7.25-7.35 (m, 2H), 7.52 (m, 2H), 7.88-7.96 (m, 4H), 8.04 (m, 2H), 8.31 (s, 1H). MS (DCI-NH_3) m/z 445 $(M+H)^+$. Anal. calc. for $C_{24}H_{16}FN_3O_3S$: C, 64.71; H, 3.62; N, 9.43. Found: C, 64.50; H, 3.53; N, 9.35.

Example 168

2-(5-Methyl-2-thienyl))-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62 substituting 2-bromo-5-methylthiophene in place of 4-iodo-1-fluorobenzene (yield: 0.200 g, 62%). M.p. 219-224 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 2.45 (s, 3H), 3.23 (s, 3H), 6.80 (m, 1H), 7.17 (m, 2H), 7.29 (m, 2H), 7.52 (m, 3H), 7.89 (m, 2H), 8.33 (s, 1H). MS (DCI-NH_3) m/z 441 $(M+H)^+$, 458 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{17}FN_2O_3S_2$: C, 59.99; H, 3.89; N, 6.36. Found: C, 59.90; H, 3.91; N, 6.26.

Example 169

2-(3-Biphenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62 substituting 3-bromobiphenyl in place of 4-iodo-1-fluorobenzene (yield: 0.28 g, 78%). M.p. 126-134 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 3.24 (s, 3H), 7.15 (m,

2H), 7.31 (m, 2H), 7.37-7.45 (m, 1H), 7.51 (m, 4H), 7.64 (m, 2H), 7.68-7.79 (m, 3H), 7.92 (m, 3H), 8.27 (s, 1H). MS (DCI-NH_3) m/z 497 $(M+H)^+$, 514 $(M+NH_4)^+$. Anal. calc. for $C_{29}H_{21}FN_2O_3S$: C, 70.15; H, 4.26; N, 5.64. Found: C, 69.91; H, 4.33; N, 5.74.

Example 170

2-(3,5-Dimethylphenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62 substituting 5-bromo-m-xylene in place of 4-iodo-1-fluorobenzene (yield: 0.152 g, 46.5%). M.p. 130-134 °C. ^1H NMR (300 MHz, DMSO d_6) δ 2.34 (s, 6H), 3.23 (s, 3H), 7.07-7.12 (m, 2H), 7.15 (m, 1H), 7.21-7.32 (m, 4H), 7.52 (m, 2H), 7.90 (m, 2H), 8.29 (s, 1H). MS (DCI-NH_3) m/z 449 $(M+H)^+$, 466 $(M+NH_4)^+$. Anal. calc. for $C_{25}H_{21}FN_2O_3S$: C, 66.95; H, 4.72; N, 6.25. Found: C, 66.81; H, 4.57; N, 6.07.

Example 171

2-(3,4-Difluorophenyl)-4-(4-fluorobenzyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

4-(4-Fluorophenylmethyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone was prepared according to the method of Example 11, starting with 2-benzyl-4-(4-fluorophenylmethyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 0.3319 g, 83%).

The title compound was prepared according to the method of Example 62 substituting 4-(4-fluorophenylmethyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting 1-bromo-3,4-difluorobenzene in place of 4-iodo-1-fluorobenzene (yield: 0.085 g, 54%). M.p. 157-159 °C. ^1H NMR (300 MHz, DMSO d_6) δ 3.30 (s, 3H), 3.88 (bs, 2H), 7.04 (m, 4H), 7.49-7.66 (m, 2H), 7.70 (m, 2H), 7.81 (m, 1H), 8.12 (s, 1H). MS (DCI-NH_3) m/z 471 $(M+H)^+$, 488 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{17}F_3N_2O_3S \cdot 0.25\ H_2O$: C, 60.69; H, 3.71; N, 5.84. Found: C, 6.39; H, 3.76; N, 5.81.

Example 172

2-(3-Chloro-4-fluorophenyl)-4-(4-fluorobenzyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62 substituting 4-(4-fluorophenylmethyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting 4-bromo-2-chloro-1-fluorobenzene in place of 4-iodo-1-fluorobenzene (yield: 0.110 g, 74%). M.p. 153-156 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 3.30 (s, 3H), 3.89 (bs, 2H), 7.02-7.07 (m, 4H), 7.59 (m, 1H), 7.65-7.72 (m, 4H), 8.07 (m, 2H), 8.12 (s, 1H). MS (DCI-NH_3) m/z 487 $(M+H)^+$, 504 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{17}ClF_2N_2O_3S\cdot 0.25\ H_2O$: C, 58.65; H, 3.58; N, 5.64. Found: C, 58.41; H, 3.56; N, 5.36.

Example 173

2-(2-Thienyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62 substituting 2-bromothiophene in place of 1-bromo-4-fluorobenzene (yield: 98 mg, 40%). M.p. 215-217 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.25 (s, 3H), 7.18 (m, J = 9 Hz, 3H), 7.29 (m, 2H), 7.42 (d, 2H), 7.75 (d, 1H), 7.93 (d, J = 9 Hz), 8.4 (s, 1H). MS (DCI-NH_3) m/z 427 $(M+H)^+$, 444 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{15}FN_2O_3S_2$: C, 59.14; H, 3.54; N, 6.57.

Example 174

2-(4-Trifluoromethylphenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62 substituting 1-bromo-4-trifluoromethylbenzene in place of 1-bromo-4-fluorobenzene (yield: 185 mg, 64%). M.p. 171-173 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.25 (s, 3H), 7.18 (t, 2H), 7.29 (m, 2H), 7.52 (d, J = 9 Hz 2H), 7.91 (d, J = 9 Hz, 2H), 7.93 (s, 4H), 8.32 (s, 1H). MS (DCI-NH_3) m/z 489 $(M+H)^+$, 506 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{16}F_4N_2O_3S$: C, 59.02; H, 3.3; N, 5.74. Found: C, 58.75; H, 3.35; N, 5.69.

Example 175

2-[4-(1-Pyrroyl)phenyl]-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62 substituting 1-(4-iodophenyl)pyrrole in place of 1-bromo-4-fluorobenzene (yield: 140 mg, 50%). M.p. 229-231 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.25 (s, 3H), 6.3 (t, 2H), 7.18 (t, 2H), 7.29 (m, 2H), 7.46 (t, 2H) 7.53 (d, J = 9 Hz 2H), 7,75 (s, 4H), 7.91 (d, J = 9 Hz, 2H), 8.27 (s, 1H). MS (DCI-NH_3) m/z 486 $(M+H)^+$, 504 $(M+NH_4)^+$. Anal. calc. for $C_{27}H_{20}FN_3O_3S{\cdot}0.5\ H_2O$: C, 66.79; H, 4.15; N, 8.65. Found: C, 65.21; H, 4.29; N, 8.12.

Example 176

2-(5-Chloro-2-thienyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62 substituting 1-bromo-5-chlorothiophene in place of 1-bromo-4-fluorobenzene (yield: 225 mg, 93%). M.p. 190-192 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.38 (s, 3H), δ 3.25 (s, 3H), 7.15 (t, 2H), 7.29 (m, 4H), 7.5 (D, 4H) 7.91 (d, J = 9 Hz, 2H), 8.21 (s, 1H). MS (DCI-NH_3) m/z 435 $(M+H)^+$, 452 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{19}F\ N_2O_3S$: C, 66.35; H, 4.41; N, 6.45. Found: C, 66.15; H, 4.37; N, 6.3.

Example 177

2-(4-Methylphenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62 substituting 1-bromo-4-methylbenzene in place of 1-bromo-4-fluorobenzene (yield: 79 mg, 31%). M.p. 190-192 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.38 (s, 3H), δ 3.25 (s, 3H), 7.15 (t, 2H), 7.29 (m, 4H), 7.5 (D, 4H) 7.91 (d, J = 9 Hz, 2H), 8.21 (s, 1H). MS (DCI-NH_3) m/z 435 $(M+H)^+$, 452 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{19}F\ N_2O_3S$: C, 66.35; H, 4.41; N, 6.45. Found: C, 66.15; H, 4.37; N, 6.3.

Example 178

2-(4-Fluorophenyl)-4-(2-ethyl-1-hexyloxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

To a solution of 2-ethyl-1-hexanol (65 mg, 0.5 mmol) in THF (15 mL) at room temperature was added NaH (60% oil suspension) (20 mg, 0.5 mmol) and after 10 minutes 2-(4-fluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (193 mg, 0.5 mmol) was added. The resulting mixture was stirred at room temperature for the next 2 hours. The mixture was quenched with 10% citric acid and extracted with ethyl acetate. The extract was washed with water, brine, dried with $MgSO_4$, and purified by chromatography (silica gel, 2:1 hexanes-ethyl acetate) to provide the desired product (yield: 140 mg, 60%). M.p. 120-122 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 0.75 (m, 6H), 1.1 (m, 6H), 1.20 (quintet, J = 7 Hz, 2H), 1.44 (m, 1H), 3.27 (s, 3H), 4.30 (d, J = 6 Hz, 2H), 7.37 (t, J = 9 Hz, 2H), 7.65 (m, 2H), 7.89 (d, J = 9 Hz, 2H), 8.06 (d, J = 9 Hz, 2H), 8.18 (s, 1H). MS (APCI+) m/z 473 $(M+H)^+$; (APCI-) m/z 507 $(M+Cl)^-$. Anal. calc. for $C_{25}H_{29}FN_2O_4S{\cdot}0.5\ H_2O$: C, 62.35; H, 6.27; N, 5.87. Found: C, 62.22; H, 6.14; N, 6.22.

Example 179

2-(3-Thienyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62 substituting 3-bromothiophene in place of 1-bromo-4-fluorobenzene (yield: 225 mg, 93%). M.p. 200-202 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 3.25 (s, 3H), 7.15 (t, 2H), 7.29 (m, 2H), 7.5 (d, J = 9 Hz, 2H), 7.6 (M, 1H) 7.66 (dd, 1H), 7.91 (d, J = 9 Hz, 2H), 8.13 (dd, 1H), 8.25 (s, 1H). MS (DCI-NH_3) m/z 427 $(M+H)^+$, 444 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{15}FN_2O_3S_2$: C, 55.07; H, 4.07; N, 6.11. Found: C, 54.63; H, 3.47; N, 6.01.

Example 180

2-(3,5-Difluorophenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62 substituting 3,5-difluorobromobenzene in place of 1-bromo-4-fluorobenzene (yield:

250 mg, 96%). M.p. 166-168 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 3.25 (s, 3H), δ 7.15 (t, 2H), 7.27 (m, 2H), 7.4 (m, 1H), 7.41 (m, 2H), 7.51 (d, J = 9 Hz, 4H), 7.9 (d, J = 9 Hz, 2H), 8.3 (s, 1H). MS (DCI-NH_3) m/z 457 $(M+H)^+$, 474 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{15}F_3N_2O_3S$: C, 60.13; H, 3.31; N, 6.14. Found: C, 60.49; H, 3.31; N, 6.03.

Example 181

2-(2,4-Difluorophenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62 substituting 2,4-difluorobromobenzene in place of 1-bromo-4-fluorobenzene (yield: 40 mg, 15%). M.p. 245-247 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 3.23 (s, 3H), δ 7.15 (t, 2H), 7.3 (t, 2H), 7.54 (m, 2H), 7.57 (m, 2H), 7.75 (m, 1H), 7.9 (d, J = 9 Hz, 2H), 8.27 (s, 1H). MS (DCI-NH_3) m/z 457 $(M+H)^+$, 474 $(M+NH_4)^+$. Anal. calc. for $C_{28}H_{15}F_3N_2O_3S$: C, 60.52; H, 3.31; N, 6.03.

Example 182

2-(3,4-Difluorophenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62 substituting 3,4-difluorobromobenzene in place of 1-bromo-4-fluorobenzene (yield: 170 mg, 70%). M.p. 109-110 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 3.23 (s, 3H), δ 7.15 (t, 2H), 7.3 (t, 2H), 7.25 (m, 2H), 7.59 (m, 4H), 7.83 (m, 1H), 7.9 (d, J = 9 Hz, 2H), 8.27 (s, 1H). MS (DCI-NH_3) m/z 457 $(M+H)^+$, 474 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{15}F_3N_3O_3S$: C, 60.52; H, 3.31; N, 6.14. Found 60.60; H, 3.48; N, 5.89

Example 183

2-(3-Furyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62 substituting 3-bromofuran in place of 1-bromo-4-fluorobenzene (yield: 175 mg, 73%). M.p. 239-242 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 3.25 (s, 3H), 7.09 (d, 1H), 7.15 (t, 2H), 7.29 (m, 2H), 7.5 (d, J = 9 Hz 2H), 7.8 (t, 1H) 7.91 (d, J = 9 Hz, 2H), 8.3 (s 1H), 8.58 (s, 1H). MS (DCI-NH_3) m/z 411 $(M+H)^+$, 428 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{15}F N_2O_4S \cdot 0.5\ H_2O$: C, 61.46; H, 3.68; N, 6.83. Found: C, 59.91; H, 3.54; N, 6.54.

Example 184

2-(3-Fluoro-4-methoxyphenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62 substituting 3-fluoro-4-methoxybromobenzene in place of 1-bromo-4-fluorobenzene (yield: 230 mg, 85%). M.p. 97-101 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.25 (s, 3H), 3.9 (s, 3H), 7.16 (d, 1H), 7.29 (m, 3H), 7.5 (m, 4H), 7.91 (d, J = 9 Hz, 2H), 8.23 (s 1H). MS (DCI-NH_3) m/z 469 $(M+H)^+$, 491 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{18}F_2N_2O_4S{\cdot}0.5\ H_2O$: C, 61.53; H, 3.87; N, 5.98. Found: C, 61.18; H, 4.01; N, 5.58.

Example 185

2-(2-Fluorophenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62 substituting 2-fluorobromobenzene in place of 1-bromo-4-fluorobenzene (yield: 195 mg, 75%). M.p. 96-103 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.23 (s, 3H), δ 7.15 (t, 2H), 7.3 (m, 3H), 7.55 (m, 5H), 7.9 (d, J = 9 Hz, 2H), 8.27 (s, 1H). MS (ESI) m/z 437 $(M-H)^+$). Anal. calc. for $C_{23}H_{16}F_2N_2O_3S$: C, 63.01; H, 3.68; N, 6.39. Found, C, 62.91; H, 4.06; N, 5.99.

Example 186

2-[4-(Aminosulfonyl)phenyl]-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62 substituting 4-aminosulfonyl-1-bromobenzene in place of 1-bromo-4-fluorobenzene. M.p. 213-216 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.25 (s, 3H), 7.15 (t, 2H), 7.29 (m, 2H), 7.53 (s, 2H) 7.55 (s, 1H), 7.7 (dd, 2H) 7.91 (t, 4H), 7.98 (d, 2H), 8.3 (s, 1H). MS (DCI-NH_3) m/z 499 $(M+H)^+$, 517 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{18}FN_3O_5S_2{\cdot}0.5\ H_2O$: C, 55.30; H, 3.63; N, 8.41. Found: C, 54.4; H, 3.79; N, 7.78.

Example 187

2-(3-Chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62 substituting 3-chloro-4-fluoro-1-bromobenzene in place of 1-bromo-4-fluorobenzene (yield: 320 mg, 78%). M.p. 155-157 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.23 (s, 3H), δ 7.15 (t, 2H), 7.3 (t, 2H), 7.25 (m, 2H), 7.53 (d, J = 9 Hz, 2H), 7.59 (t, 1H), 7.73 (m, 1H), 7.9 (d, J = 9 Hz, 2H) 7.96 (m, 1H), 8.27 (s, 1H). MS (DCI-NH_3) m/z 473 $(M+H)^+$, 490 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{15}ClF_2N_2O_3S$: C, 58.42; H, 3.2; N, 5.92. Found 58.23; H, 2.87; N, 5.70

Example 188

2-(3,5-Dichlorophenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62 substituting 3,5-dichlorobenzene in place of 1-bromo-4-fluorobenzene (yield: 360 mg, 78%). M.p. 289-294 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.25 (s, 3H), δ 7.15 (t, 2H), 7.27 (m, 2H), 7.51 (d, J = 9 Hz, 4H), 7.75 (t, 1H), 7.83 (d, 2H), 7.9 (d, J = 9 Hz, 2H), 8.3 (s, 1H). MS (DCI-NH_3) m/z 490 $(M+H)^+$, 507 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{15}Cl_2FN_2O_3S \cdot 0.5\ H_2O$: C, 56.45; H, 3.09; N, 5.72. Found: C, 55.36; H, 3.00; N, 5.50.

Example 189

2-(4-Fluoro-3-methylphenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62 substituting 1-bromo-4-fluoro-3-methylbenzene in place of 1-bromo-4-fluorobenzene (yield: 275 mg, 71%). M.p. 168-170 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.3 (s, 3H), δ 3.25 (s, 3H), 7.15 (t, 2H), 7.3 (m, 3H), 7.56 (m, 4H), 7.9 (d, 2H), 8.23 (s, 2H). MS (DCI-NH_3) m/z 453 $(M+H)^+$, 471 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{18}F_2N_2O_3S$: C, 63.71; H, 4.01; N, 6.01. Found: C, 63.53; H, 4.06; N, 5.92.

Example 190

2-(4-Chloro-3-fluorophenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone:

The title compound was prepared according to the method of Example 62 substituting 4-bromo-1-chloro-2-fluorobenzene in place of 1-bromo-4-fluorobenzene (yield: 220 mg, 80%). M.p. 102-110 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.23 (s, 3H), 7.11-7.19 (m, 2H), 7.25-7.32 (m, 2H), 7.51 (d, J = 5.6 Hz, 2H), 7.58-7.64 (m, 1H), 7.75-7.87 (m, 2H), 7.91 (d, J = 5.6 Hz, 2H), 8.28 (s, 1H). MS (APCI+) m/z 473 $(M+H)^+$.

Example 191

2-(4-Chloro-2-fluorophenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone:

The title compound was prepared according to the method of Example 62 substituting 1-bromo-4-chloro-2-fluorobenzene in place of 1-bromo-4-fluorobenzene (yield: 65 mg 24%). M.p. 250-260 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.21 (s, 3H), 7.12-7.19 (m, 2H), 7.25-7.32 (m, 2H), 7.49-7.58 (m, 3H), 7.68-7.78 (m, 2H), 7.91 (d, J = 8.7 Hz, 2H), 8.29 (s, 1H). MS (APCI+) m/z 473 $(M+H)^+$. Anal. calc. for $C_{23}H_{15}ClF_2N_2O_3S$: C, 58.41; H, 3.19; N, 5.92. Found: C, 58.69; H, 3.45; N, 5.78.

Example 192

2-(1-Adamantyloxycarbonyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A solution of 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, prepared according to the procedure of Example 11 (200 mg, 0.58 mmol) in CH_2Cl_2 (8 ml) was prepared and stirred. 1-Adamantylfluoroformate (172 mg, 0.87 mmol), dimethylaminopyridine (14 mg, 0.011 mmol) and triethylamine (0.12 ml, 0.87 mmol) were added. The reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 (50 ml) and washed with 10% citric acid (50 ml), brine (50 ml) and dried over $MgSO_4$, and concentrated *in vacuo.* The resulting crude residue was purified using flash chromatography (SiO_2, eluting with 15:1 CH_2Cl_2:diethyl ether) to provide the desired product (yield: 55 mg, 18%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.66 (bs, 6H), 2.25 (bd, 10H), 3.21 (s, 3H), 7.15 (t, 2H), 7.24 (m, 2H), 7.6 (dd, 2H), 7.88 (d, J =

9 Hz, 2H), 8.15 (s, 1H). MS (ESI) m/z 521 (M-H)+. Anal. calc. for $C_{21}H_{15}F N_2O_3S_2$: C, 64.35; H, 5.20; N, 5.36.

Example 193

2-(2,2,2-Trifluoroethyl)-4-(4-fluorobenzyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

193A. 2-(2,2,2-Trifluoroethyl)-4,5-dichloro-3(2H)-pyridazinone

2,2,2-Trifluoroethylhydrazine (70% solution in water, 35.0 g, 0.307 mol) was treated with mucochloric acid (51.88 g, 0.307 mol) in ethanol (300 mL) and refluxed for 5 hours. The solvent was concentrated *in vacuo*. The crystals obtained were washed with water and air dried (yield: 50 g; 67.5%). ^1H NMR (300 MHz, $CDCl_3$) d 4.8 (q, J = 9 Hz, 2H), 7.85 (s, 1H). MS (DCI-NH_3) m/z 264 (M+NH4)+.

193B. 2-(2,2,2-Trifluoroethyl)-4-chloro-5-hydroxy-3(2H)-pyridazinone

2-(2,2,2-Trifluoroethyl)-4,5-dichloro-3(2H)-pyridazinone (15.0 m 60.7 mmol), and potassium carbonate (10 g, 72.4 mmol.) were mixed with water (500 mL) and stirred at reflux for 6 hours. TLC (1:1:2 CH_2Cl_2/hexanes/ethyl acetate) indicated that all starting material was consumed.) The reaction mixture was cooled to room temperature. The pH of the reaction mixture was adjusted to about 4 with hydrochloric acid (15%). The product was extracted with ethyl acetate (700 mL). The organic phase was washed with brine, dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The hydroxy compound was obtained as a light brown solid (yield: 13.1 g, 94%). ^1H NMR (300 MHz, DMSO-d_6) δ 4.92 (q, J = 9 Hz, 2H), 7.9 (s, 1H). MS (DCI-NH_3) m/z 229 (M+H)+.

193C. 2-(2,2,2-Trifluoroethyl)-4-chloro-5-(trifluoromethylsulfonyloxy)-3(2H)-pyridazinone

Anhydrous Na_2CO_3 (9.04 m, 85.32 mmol) was placed in a 500 mL round bottom flask and anhydrous CH_2CL_2 (200 mL) was added. The reaction mixture was cooled to 0 ^oC under N_2. The halohydroxy pyridazinone prepared in Example 193B was dissolved in CH_2CL_2 (100 mL) and added slowly to the flask and stirred overnight. The reaction slowly warmed to room temperature. (TLC (2: 1 hexanes/ethyl acetate) indicated completion of the reaction.) The reaction was quenched with H_2O. The organic phase containing the product was separated, washed with brine and dried over $MgSO_4$. The resulting filtrate was concentrated under reduced pressure. The crude product was isolated as deep red-brown

residue. Purification using a silica gel column (30:70 ethyl acetate/pentanes) provided the title compound as a dark, reddish residue (14.3 m, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.85 (q, J = 9 Hz, 2H), 7.9 (s, 1H). MS (DCI-NH_3) m/z 378 $(M+NH_4)^+$.

193D. 2-(2,2,2-Trifluoroethyl)-4-chloro-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone

A solution of the triflate prepared in Example 193C (1.56 g 4.3 mmol), 4-(methylthio)phenylboronic acid (870 mg, 5.16 mmol), tetrakis(triphenylphosphine)-palladium(0) (250 mg, 5% mmol) and triethylamine (1.44 ml, 10.32 mmol) in toluene was heated at reflux for 1 hour. The mixture was partitioned between ethyl acetate and water. The ethyl acetate layer was washed with water, then brine, followed by drying over $MgSO_4$ and filtration. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 92:8 hexanes/ethyl acetate) to provide the coupled intermediate as a pale, greenish-yellow solid (yield: 500 mg, 35%). M.p. 130-139 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.55 (s, 3H), 4.87 (q, J = 9 Hz, 2H), 7.37 (d, J = 9 Hz, 2H), 7.48 (d, J = 9 Hz, 2H), 7.82 (s, 1H). MS (DCI-NH_3) m/z 335 $(M+H)^+$.

193E. 2-(2,2,2-Trifluoroethyl)-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 10, substituting the coupled intermediate prepared in Example 193D in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (yield: 440 mg, 81%). M.p. 221-222 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.33 (s, 3H), 5.10 (q, J = 9 Hz, 2H), 7.90 (d, J = 9 Hz, 2H), 8.12 (d, J = 9 Hz, 2H), 8.20 (s, 1H). MS (DCI-NH_3) m/z 367 $(M+H)^+$.

193F. 2-(2,2,2-Trifluoroethyl)-4-(4-fluorobenzyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

Magnesium turnings (500 mg) were placed in a dry 250 mL round bottom flask. Anhydrous ether (20 mL) was added under N_2 at room temperature then fluorobenzyl bromide (3 mL) was added and stirred. The reaction was heated at 40 ^{o}C for 2 hours. All magnesium was consumed resulting in a pale brownish-yellow solution. The 2-(2,2,2-trifluoroethyl)-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone prepared in Example 193E was dissolved in dry THF (25 mL) and transferred to the Grignard solution. The mixture was heated for 3 hours. TLC (2:1 hexanes/ethyl acetate) indicated that the pyridazinone starting material was consumed.) The reaction was cooled to room temperature then quenched with a

saturated NH_4Cl solution. The product was extracted with ethyl acetate (250 mL); and the organic layer was washed with saturated NH_4Cl, and brine. The ethyl acetate solution was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The product was isolated as an orange residue. Purification using a silica gel column (20:80 ethyl acetate/pentanes) provided the title compound as a pale yellow powder (yield: 140 mg, 28%). ^1H NMR (300 MHz, $CDCl_3$) δ 3.13 (s, 3H), 4.85 (m, 2H), 6..93 (m, 4H), 7.49 (d, J = 9 Hz, 2H) 7.72 (s, 1H), 8.08 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 441 $(M+H)^+$. Anal. calc. for $C_{20}H_{16}F_4N_2O_3S{\cdot}0.5\ H_2O$: C, 53.45; H, 3.81; N, 6.23. Found C, 53.45; H, 3.81; N, 6.23.

Example 194

2-(4-Fluorophenyl)-4-(4-fluorophenoxymethyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

194A. 2-(4-Fluorophenyl)-4,5-dibromo-3(2H)-pyridazinone

Mucobromic acid (5.0 g, 19.4 mmol) dissolved in acetic acid (110 mL) was treated with 4-fluorophenyl hydrazine·HCl, and the heterogeneous mixture brought to reflux at a bath temperature of 115 °C for 15 hours. During the course of reaction, the mixture became a homogeneous deep red solution, and upon cooling to 23 °C, a crystalline precipitate formed. The solution was poured into ice water (1000 mL) and stirred for 20 minutes. The yellow/brown crystals were filtered off, washed with additional cold water, and dried *in vacuo* to provide 5.8 g (86%) of product. (*J. Het. Chem..*, **1993**, *30*, 1501; *Heterocycles* 1985, *23*, 2603) ^1H NMR (300 MHz, DMSO-d_6) δ 7.31-7.41 (m, 2H), 7.57-7.64 (m, 2H), 8.29 (s, 1H). MS (DCI+) m/z 347 $(Br_{79}Br_{79}\ M+H)^+$, m/z 349 $(Br_{79}Br_{81}\ M+H)^+$, m/z 364 $(Br_{79}Br_{79}\ M+NH_4)^+$, and m/z 366 $(Br_{79}Br_{81}\ M+NH_4)^+$.

194B. 2-(4-Fluorophenyl)-4-methoxy-5-bromo-3(2H)-pyridazinone

A 23 °C homogeneous solution of 2-(4-fluorophenyl)-4,5-dibromo-3(2H)-pyridazinone (7.18 g, 20.6 mmol) prepared above in tetrahydrofuran (322 mL) was treated with methanol (0.843 mL, 20.8 mmol) and after 5 minutes with NaH (0.833 g, 20.8 mmol, 60% oil dispersion). The reaction exothermed for several minutes and then was continued for 8 hours at 23 °C (Note: several reactions have run to completion at this point). The reaction did not run to completion, and so the temperature was raised to reflux for 4 hours more. The reaction was still not completed. An additional 0.1 equivalent of NaOMe solution was prepared in a separate flask as above with the quantities: 32 mL of tetrahydrofuran, 0.084 mL of

methanol, and 83 mg of 60% NaH oil dispersion. This NaOMe solution was added via syringe to the reaction mixture cooled to 23 °C, and then the temperature raised to reflux for 4 hours The reaction was still not complete, and so another 0.1 equivalent NaOMe solution was prepared, added, and the reaction brought to reflux, as above. After this 4 hours, the reaction was completed. The mixture was cooled to 23 °C and diluted to 2000 mL with water. The yellow/white precipitate that formed was filtered off, washed with additional water, and concentrated *in vacuo* to provide 5.39 g (88%) of product. (*J. Het. Chem.*, **1988**, *25*, 1757) ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.13 (s, 3H), 7.30-7.40 (m, 2H), 7.56-7.62 (m, 2H), 8.22 (s, 1H). MS (APCI+) m/z 299 (Br_{79} M+H)$^+$ and m/z 301 (Br_{81} M+H)$^+$.

194C. <u>2-(4-Fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone</u>

The title compound was prepared according to the method of Example 6 starting with 2-(4-fluorophenyl)-4-methoxy-5-bromo-3(2H)-pyridazinone in place of 2-benzyl-4-bromo-5-methoxy-3(2H)-pyridazinone and substituting 4-(methylthio)-benzeneboronic acid in place of 4-fluorobenzeneboronic acid (yield: 70 mg, 61%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.54 (s, 3H), 4.02 (s, 3H), 7.35 (dd, J = 9.0, 9.0 Hz, 2H), 7.39 (d, J = 8.5 Hz, 2H), 7.61 (d, J = 8.5 Hz, 2H), 7.65 (dd, J = 9.0, 5.0 Hz, 2H), 8.14 (s, 1H). MS (APCI+) m/z 343 (M+H)$^+$.

194D. <u>2-(4-Fluorophenyl)-4-methyl-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone</u>

The title compound was prepared according to the method of Example 228 substituting methyl magnesium bromide in place of cyclohexylmagnesium chloride (yield: 0.83 g, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.25 (s, 3H), 2.55 (s, 3H), 7.17 (dd, J = 8.8, 8.8 Hz, 2H), 7.31 (d, J = 8.7 Hz, 2H), 7.38 (d, J = 8.7 Hz, 2H), 7.61-7.68 (m, 2H), 7.82 (s, 1H). MS (APCI+) m/z 327 (M+H)$^+$.

194E. <u>2-(4-Fluorophenyl)-4-methyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone</u>

The title compound was prepared according to the method of Example 10 substituting 2-(4-fluorophenyl)-4-methyl-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (yield: 473 mg, 86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.24 (s, 3H), 3.14 (s, 3H), 7.19 (dd, J = 8.8, 8.8 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.63-7.69 (m, 2H), 7.80 (s, 1H), 8.12 (d, J = 8.4 Hz, 2H). MS (APCI+) m/z 359 (M+H)$^+$ and m/z 376 ($M+NH_4$)$^+$.

194F. 2-(4-Fluorophenyl)-4-bromomethyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

To a heterogeneous, refluxing solution of 2-(4-fluorophenyl)-4-methyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (590 mg, 1.65 mmol) and carbon tetrachloride (24 mL) was quickly added *N*-bromosuccinimide (yield: 308 mg, 1.73 mmol) followed by benzoyl peroxide (12 mg, 0.05 mmol). After 1 hour the reaction had only run to near 50% completion. Additional benzoyl peroxide (12 mg, 0.05 mmol) was added, and the reaction checked after another 1 hour. The reaction was still not complete, and so more benzoyl peroxide (4 mg, 0.017 mmol) was added. After 30 minutes, the reaction was completed. The mixture was cooled to 23 °C and diluted with ethyl acetate. The acetate solution was washed with saturated $NaHCO_3$, water, and brine. The solution was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was chromatographed (flash silica gel, ethyl acetate/hexanes gradient 1:1 to 4:1) to provide the product (yield: 530 mg, 74%). ^1H NMR (300 MHz, $CDCl_3$) δ 3.16 (s, 3H), 4.34 (s, 2H), 7.20 (dd, J = 8.8, 8.8 Hz, 2H), 7.67-7.74 (m, 2H), 7.82 (d, J = 8.7 Hz, 2H), 7.86 (s, 1H), 8.17 (d, J = 8.7 Hz, 2H). MS (APCI+) m/z 437 $(M+H)^+$.

194G. 2-(4-Fluorophenyl)-4-(4-fluorophenoxymethyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

To a homogeneous solution of 2-(4-fluorophenyl)-4-bromomethyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, prepared above, (107 mg, 0.246 mmol) and 4-fluorophenol (30.3 mg, 0.270 mmol) dissolved in acetone (4 mL) was added powdered K_2CO_3 (37.3 mg, 0.270 mmol). The mixture was stirred at 23 °C for 2 hours, filtered through a bed of Celite®, and concentrated *in vacuo*. The residue was chromatographed (flash silica gel, ethyl acetate/hexanes 3:2) to provide the product (yield: 83 mg, 72%). M.p. 65-80 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.12 (s, 3H), 4.94 (s, 2H), 6.78-6.86 (m, 2H), 6.91-7.00 (m, 2H), 7.15-7.24 (m, 2H), 7.65-7.72 (m, 2H), 7.74 (d, J = 8.7 Hz, 2H), 7.93 (s, 1H), 8.08 (d, J = 8.7 Hz, 2H). MS (APCI+) m/z 469 $(M+H)^+$. Anal. calc. for $C_{24}H_{18}F_2N_2O_4S$: C, 61.53; H, 3.87; N, 5.97. Found: C, 61.22; H, 3.63; N, 5.64.

Example 195

2-(4-Fluorophenyl)-4-(3-fluorophenoxymethyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 194G substituting 3-fluorophenol in place of 4-fluorophenol (yield: 94 mg, 88%). M.p. 142-144 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.12 (s, 3H), 4.98 (s, 2H), 6.49-6.56 (m, 1H), 6.60-6.73 (m, 2H), 7.15-7.25 (m, 3H), 7.65-7.75 (m, 4H), 7.93 (s, 1H), 8.07 (d, J = 8.7 Hz, 2H). MS (APCI+) m/z 469 $(M+H)^+$. Anal. calc. for $C_{24}H_{18}F_2N_2O_4S$: C, 61.53; H, 3.87; N, 5.97. Found: C, 61.20; H, 3.92; N, 5.86.

Example 196

2-(4-Fluorophenyl)-4-phenoxymethyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 294G substituting phenol in place of 4-fluorophenol (yield: 67 g, 93%). M.p. 42-75 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 3.28 (s, 3H), 4.92 (s, 2H), 6.83-6.90 (m, 2H), 6.91-6.99 (m, 1H), 7.22-7.30 (m, 2H), 7.35-7.44 (m, 2H), 7.66-7.73 (m, 2H), 7.81-7.88 (m, 2H), 8.02-8.08 (m, 2H), 8.21 (s, 1H). MS (APCI+) m/z 451 $(M+H)^+$.

Example 197

2-(4-Fluorophenyl)-4-(*t*-butylthiomethyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A 0 °C solution of the 2-(4-fluorophenyl)-4-bromomethyl-5-[4-(methyl-sulfonyl)phenyl]-3(2H)-pyridazinone prepared in Example 194F (92.5 mg, 0.212 mmol) in acetone (2.5 mL) was treated with NaI (35 mg, 0.233 mmol), and after 5 minutes, the cooling bath was removed and the reaction warmed to 23 °C. After 30 minutes, conversion to the 2-(4-fluorophenyl)-4-iodomethyl-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone was complete (thin layer chromatography, ethyl acetate/hexanes 4:1). The NaBr and residual NaI were filtered off through a pad of Celite®. Additional acetone (2 mL) was added along with 2-methyl-2-propanethiol (20.5 mg, 0.227 mmol), and the solution cooled to 0 °C before addition of Ag_2CO_3 (63 mg, 0.227 mmol). After 5 minutes, the cooling bath was removed and the solution warmed to 23 °C for 5 hours. The reaction mixture was filtered through Celite® and concentrated *in vacuo*. The residue was chromatographed (flash silica gel, ethyl acetate/hexanes gradient 1:1 to 3:2) to provide the product (yield: 57 mg, 60%). M.p. 50-70 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 9H), 3.14 (s, 3H), 3.65

(s, 2H), 7.13-7.21 (m, 2H), 7.63-7.70 (m, 2H), 7.79 (s, 1H), 7.84 (d, J = 8.7 Hz, 2H), 8.13 (d, J = 8.7 Hz, 2H). MS (APCI+) m/z 447 $(M+H)^+$. Anal. calc. for $C_{22}H_{23}FN_2O_3S_2$: C, 59.17; H, 5.19; N, 6.27. Found: C, 59.48; H, 5.36; N, 5.90.

Example 198

2-(4-Fluorophenyl)-4-(2-methylpropylthiomethyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 197 substituting 2-methyl-1-propanethiol in place of 2-methyl-2-propanethiol (yield: 66 mg, 70%). M.p. 45-60 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (d, J = 6.6 Hz, 6H), 1.67-1.82 (m, 1H), 2.62 (d, J = 6.6 Hz, 2H), 3.15 (s, 3H), 3.61 (s, 2H), 7.19 (dd, J = 8.2, 8.2 Hz, 2H), 7.62-7.71 (m, 2H), 7.75 (d, J = 8.4 Hz, 2H), 7.79 (s, 1H), 8.13 (d, J = 8.4 Hz, 2H). MS (APCI+) m/z 447 $(M+H)^+$. Anal. calc. for $C_{22}H_{23}FN_2O_3S_2$: C, 59.17; H, 5.19; N, 6.27. Found: C, 59.35; H, 5.25; N, 6.05.

Example 199

2-(4-Fluorophenyl)-4-(2-propoxy)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone

The title compound was prepared by the following sequence of reactions. Mucobromic acid and 4-fluorophenylhydrazine hydrochloride were reacted to provide 2-(4-fluorophenyl)-4,5-dibromo-3(2H)-pyridazinone following the procedure in Example 194A. The dibromo-intermediate was reacted according to the procedure described in Example 194B, substituting isopropanol in place of methanol, to selectively react at the 4-position and provide 2-(4-fluorophenyl)-4-(2-propoxy)-5-bromo-3(2H)-pyridazinone.

The 5-bromo-compound was coupled to 4-(methylthio)phenylboronic acid according to the method of Example 6 to provide the title compound (yield: 435 mg, 53.9%). M.p. 135-137 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (d, J = 6 Hz, 6H), 2.55 (s, 3H), 5.26 (sept, J = 6 Hz, 1H), 7.17 (t, J = 9 Hz, 2H), 7.34 (d, J = 9 Hz, 2H), 7.57 (d, J = 9 Hz, 2H), 7.58-7.66 (m, 2H), 7.95 (s, 1H). MS (DCI-NH_3) m/z 371 $(M+H)^+$.

Example 200

2-(4-Fluorophenyl)-4-(2-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The methyl sulfide compound prepared in Example 199 was oxidized according to the method of Example 10 to provide the title compound (yield: 240 mg, 92%). M.p. 160-162 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.30 (d, J = 6 Hz, 6H), 3.41 (s, 3H), 5.41 (m, 1H), 7.48 (t, J = 9 Hz, 2H), 7.77 (dd, J = 9 Hz, 6 Hz, 2H),

8.05 (d, J = 9 Hz, 2H), 8.19 (d, J = 9 Hz, 2H), 8.31 (s, 1H). MS (DCI-NH_3) m/z 403 $(M+H)^+$, 420 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{19}FN_2O_4S$: C, 59.70; H, 4.73; N, 6.97. Found: C, 59.40; H, 4.86; N, 6.69.

Example 201

2-(3-Chlorophenyl)-4-(2-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(3-Chlorophenyl)-4-(2-propoxy)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone was prepared according to the method of Example 199, substituting 3-chlorophenylhydrazine hydrochloride in place of 4-fluorophenylhydrazine hydrochloride, in the first step. The resulting methyl sulfide was oxidized according to the method of Example 10 to provide the title compound (yield: 260 mg, 80%). M.p. 134-136 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (d, J = 6 Hz, 6H), 3.13 (s, 3H), 5.48 (sept, J = 6 Hz, 1H), 7.37-7.48 (m, 2H), 7.59 (dt, J = 7 Hz, 1.5 Hz, 1H), 7.70 (br s, 1H), 7.84 (d, J = 9 Hz, 2H), 7.93 (s, 1H), 8.06 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 419 $(M+H)^+$, 436 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{19}ClN_2O_4S$: C, 57.42; H, 4.55; N, 6.70. Found: C, 57.08; H, 4.59; N, 6.44.

0

Example 202

2-(3-Fluorophenyl)-4-(2-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The methyl sulfide intermediate was prepared according to the method of Example 199, substituting 3-fluorophenylhydrazine hydrochloride in place of 4-fluorophenylhydrazine hydrochloride in the first step. The resulting methyl sulfide compound was oxidized according to the method of Example 10 to provide the title compound (yield: 290 mg, 72%). M.p. 110-112 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (d, J = 6 Hz, 6H), 3.11 (s, 3H), 5.47 (sept, J = 6 Hz, 1H), 7.09-7.18 (m, 1H), 7.41-7.52 (m, 3H), 7.83 (d, J = 9 Hz, 2H), 7.93 (s, 1H), 8.08 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 403 $(M+H)^+$, 447 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{19}FN_2O_4S$: C, 59.70; H, 4.73; N, 6.97. Found: C, 59.54; H, 4.87; N, 6.70.

Example 203

2-(3-Bromophenyl)-4-(2-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The methyl sulfide intermediate was prepared according to the method of Example 199, substituting 3-bromophenylhydrazine hydrochloride in place of 4-fluorophenylhydrazine hydrochloride. The resulting methyl sulfide compound was oxidized according to the method of Example 10 to provide the title compound (yield: 75 mg, 77.6%). M.p. 130-132 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (d, J =

6 Hz, 6H), 3.15 (s, 3H), 5.48 (sept, J = 6 Hz, 1H), 7.38 (t, J = 9 Hz, 1H), 7.55 (br d, J = 7 Hz, 1H), 7.65 (br d, J = 7 Hz, 1H), 7.79-7.87 (m, 1H), 7.83 (d, J = 9 Hz, 2H), 8.13 (s, 1H), 8.06 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 465 $(M+H)^+$, 480 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{19}BrN_2O_4S$: C, 51.84; H, 4.10; N, 6.05. Found: C, 51.95; H, 4.18; N, 5.74.

Example 204

2-(2,5-Difluorophenyl)-4-(2-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(2,5-Difluorophenyl)-4-(2-propoxy)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone was prepared according to the method of Example 199, substituting 2,5-difluorophenylhydrazine hydrochloride in place of 4-fluorophenylhydrazine hydrochloride .

The resulting methyl sulfide compound was oxidized according to the method of Example 10 to provide the title compound (yield: 390 mg, 90%). M.p. 161-164 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (d, J = 6 Hz, 6H), 3.12 (s, 3H), 5.55 (sept, J = 6 Hz, 1H), 7.12-7.29 (m, 3H), 7.82 (d, J = 9 Hz, 2H), 7.92 (s, 1H), 8.07 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 421 $(M+H)^+$, 438 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{18}F_2N_2O_4S \cdot 0.5\ H_2O$: C, 55.94; H, 4.31; N, 6.53. Found: C, 55.86; H, 4.19; N, 6.38.

Example 205

2-(3-Chloro-4-fluorophenyl)-4-(2-methylpropoxy)-5-[3-fluoro-4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone

The title compound was prepared by the following sequence of reactions. Mucobromic acid and 3-chloro-4-fluorophenylhydrazine hydrochloride were reacted to provide 2-(3-chloro-4-fluorophenyl)-4,5-dibromo-3(2H)-pyridazinone according to the method of Example 194A. The intermediate was selectively reacted at the 4-position with isobutanol and base to provide 2-(4-fluorophenyl)-4-[1-(2-methylpropoxy)]-5-bromo-3(2H)-pyridazinone according to the method of Example 194B. The 5-bromo-compound was coupled to 3-fluoro-4-(methylthio)-phenylboronic acid prepared in Example 194C according to the method of Example 6 to produce the intermediate methyl sulfide. The sulfide compound was oxidized to the title methyl sulfone according to the method of Example 10 (yield: 810 mg, 83.8%). M.p. 142-144 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, J = 6 Hz, 6H), 1.95 (sept, J = 6 Hz, 1H), 3.30 (s, 3H), 4.37 (d, J = 6 Hz, 2H), 7.26 (t, J = 9 Hz,

1H), 7.52-7.61 (m, 3H), 7.75 (dd, J = 9 Hz, 3 Hz, 1H), 7.89 (s, 1H), 8.10 (t, J = 9 Hz, 1H). MS (DCI-NH_3) m/z 469 $(M+H)^+$, 486 $(M+NH_4)^+$.

Example 206

2-(3,4-Difluorophenyl)-4-(4-fluorophenyl)-5-[3-methyl-4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

206A. 2-Methylthioanisole

A solution of 2-bromothioanisole (10.53 g, 52 mmol) in tetrahydrofuran (173 mL) was prepared and cooled to -78 °C. *n*-BuLi (21.8 mL, 54.5 mmol, 2.5 M solution in hexanes) was slowly added along the interior wall of the reaction vessel. The resultant light yellow solution was stirred for 30 minutes before methyl iodide (8.10 g, 57.1 mmol) diluted with tetrahydrofuran (6 mL) was slowly added along the interior wall of the reaction vessel. The mixture was stirred for another 30 minutes at -78 °C. The cooling bath was removed, and the mixture stirred for 1 hour. The solution was cooled to 0 °C and a saturated aqueous NH_4Cl solution added. The resultant solution was extracted several times with ethyl acetate, and the combined acetate layers washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was chromatographed (flash silica gel, ethyl acetate/hexanes 1:19) to provide the product (yield: 6.74 g, 94%). ^1H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3H), 2.46 (s, 3H), 7.02-7.09 (m, 1H), 7.12-7.22 (m, 3H).

206B. 4-Bromo-2-methylthioanisole.

To a 0 °C solution of 2-methylthioanisole (0.50 g, 3.57 mmol) in methylene chloride (40 mL) was added powdered Fe (20 mg, 0.36 mmol) followed by dropwise addition of bromine (0.58 g, 3.54 mmol). After 30 minutes, the starting material had been consumed (thin layer chromatography, hexanes). The excess bromine was quenched by adding a solution of $NaHSO_3$ and stirring for several minutes. The methylene chloride layer was separated, and the aqueous phase extracted with additional methylene chloride. The combined methylene chloride solution was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resultant oil was chromatographed (flash silica gel, ethyl acetate/hexanes 1:49) to provide the product (yield: 0.74 g, 96%). ^1H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3H), 2.45 (s, 3H), 7.00 (d, J = 8.4 Hz, 1H), 7.27-7.33 (m, 2H).

C 206C. 3-Methyl-4-(methylthio)benzeneboronic acid.

3-Methyl-4-(methylthio)benzeneboronic acid was prepared according to the method of Example 1, substituting 4-bromo-2-(methylthio)anisole in place of 4-

bromothioanisole (yield: 5.3 g, 67%). M.p. 208-210 . ^{1}H NMR **2.28** (s, 3H), 2.46 (s, 3H), 7.20 (d, J = 8.4 Hz, 1H), 7.62 (s, 1H), 7.70 (d, J = 8.4 Hz, 1H).

206D. <u>2-(3,4-Difluorophenyl)-4,5-dibromo-3(2H)-pyridazinone.</u>

The title compound was prepared according to the method of Example 194A, substituting 3,4-difluorophenyl hydrazine·HCl in place of 4-fluorophenyl hydrazine·HCl (yield: 39 g, 78%). ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 7.45 (m, 1H), 7.61 (m, 1H), 7.75 (m, 1H), 8.30 (s, 1H). MS (DCI-NH$_3$) m/z 382 (M+NH$_4$)$^+$.

206E. <u>2-(3,4-Difluorophenyl)-4-methoxy-5-bromo-3(2H)-pyridazinone.</u>

The title compound was prepared according to the method of Example 194B, substituting 2-(3,4-difluorophenyl)-4,5-dibromo-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4,5-dibromo-3(2H)-pyridazinone (yield: 15 mg, 88%). ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 4.14 (s, 3H), 7.45 (m, 1H), 7.60 (m, 1H), 7.74 (m, 1H), 8.24 (s, 1H). MS (DCI-NH$_3$) m/z 317 (M+H)$^+$ and m/z 334 (M+NH$_4$)$^+$.

206F. <u>2-(3,4-Difluorophenyl)-4-methoxy-5-[3-methyl-4-(methylthio)phenyl]-3(2H)-pyridazinone.</u>

The title compound was prepared according to the method of Example 6 starting with 2-(3,4-difluorophenyl)-4-methoxy-5-bromo-3(2H)-pyridazinone in place of 2-benzyl-4-bromo-5-methoxy-3(2H)-pyridazinone and substituting 3-methyl-4-(methylthio)benzeneboronic acid in place of 4-fluorobenzeneboronic acid (yield: 2.0 g, 85%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.39 (s, 3H), 2.53 (s, 3H), 4.11 (s, 3H), 7.22-7.32 (m, 2H), 7.34 (s, 1H), 7.42-7.50 (m, 2H), 7.55-7.64 (m, 1H), 7.92 (s, 1H). MS (APCI+) m/z 375 (M+H)$^+$.

206G. <u>2-(3,4-Difluorophenyl)-4-(4-fluorophenyl)-5-[3-methyl-4-(methylthio)phenyl]-3(2H)-pyridazinone.</u>

2-(3,4-Difluorophenyl)-4-(4-fluorophenyl)-5-[3-methyl-4-(methylthio)phenyl]-3(2H)-pyridazinone, was prepared according to the method of Example 228, starting with 2-(3,4-difluorophenyl)-4-methoxy-5-[3-methyl-4-(methylthio)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)-phenyl]-3(2H)-pyridazinone and substituting 4-fluorophenyl magnesium bromide in place of cyclohexylmagnesium chloride (yield: 330 mg, 56%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.24 (s, 3H), 2.47 (s, 3H), 6.90-7.03 (m, 6H), 7.22-7.31 (m, 2H), 7.49-7.54 (m, 1H), 7.60-7.68 (m, 1H), 8.02 (s, 1H). MS (APCI+) m/z 439 (M+H)$^+$.

206H. <u>2-(3,4-Difluorophenyl)-4-(4-fluorophenyl)-5-[3-methyl-4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone</u>.

The title compound was prepared according to the method of Example 10, substituting 2-(3,4-difluorophenyl)-4-(4-fluorophenyl)-5-[3-methyl-4-(methylthio)-

phenyl]-3(2H)-pyridazinone in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (yield: 251 mg, 82%) M.p. 80-100 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.59 (s, 3H), 3.25 (s, 3H), 7.13-7.34 (m, 5H), 7.45 (s, 1H), 7.52-7.69 (m, 2H), 7.81 (d, J = 8.4 Hz, 1H), 7.81-7.90 (m, 1H), 8.27 (s, 1H). MS (APCI+) m/z 471 $(M+H)^+$ and m/z 488 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{17}F_3N_2O_3S$: C, 61.27; H, 3.64; N, 5.95. Found: C, 61.53; H, 3.92; N, 5.67.

Example 207

2-(3-Chlorophenyl)-4-(4-fluorophenoxymethyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

207A. 2-(3-Chlorophenyl)-4,5-dibromo-3(2H)-pyridazinone.

The title compound was prepared according to the method of Example 194A, substituting 3-chlorophenyl hydrazine·HCl in place of 4-fluorophenyl hydrazine·HCl (yield: 24.8 g, 88%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.53-7.57 (m, 3H), 7.67-7.70 (m, 1H), 8.29 (s, 1H). MS (DCI-NH_3) m/z 365 $(M+H)^+$ and m/z 382 $(M+NH_4^+)^+$.

207B. 2-(3-Chlorophenyl)-4-methoxy-5-bromo-3(2H)-pyridazinone.

The title compound was prepared according to the method of Example 194B, substituting 2-(3-chlorophenyl)-4,5-dibromo-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4,5-dibromo-3(2H)-pyridazinone (yield: 12.4 g, 95%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.21 (s, 3H), 7.58-7.62 (m, 3H), 7.73-7.76 (m, 1H), 8.28 (s, 1H). MS (DCI-NH_3) m/z 317 $(M+H)^+$ and m/z 334 $(M+NH_4^+)^+$.

207C. 2-(3-Chlorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone.

The title compound was prepared according to the method of Example 6 starting with 2-(3-chlorophenyl)-4-methoxy-5-bromo-3(2H)-pyridazinone in place of 2-benzyl-4-bromo-5-methoxy-3(2H)-pyridazinone and substituting 4-(methylthio)-benzeneboronic acid in place of 4-fluorobenzeneboronic acid (yield: 3.3 g, 68%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.54 (s, 3H), 4.03 (s, 3H), 7.40 (d, J = 9.0 Hz, 2H), 7.50-7.64 (m, 5H), 7.73-7.77 (m, 1H), 8.18 (s, 1H). MS (DCI-NH_3) m/z 359 $(M+H)^+$.

207D. 2-(3-Chlorophenyl)-4-methyl-5-[3-methyl-4-(methylthio)phenyl]-3(2H)-pyridazinone.

2-(3-Chlorophenyl)-4-(4-fluorophenyl)-5-[3-methyl-4-(methylthio)phenyl]-3(2H)-pyridazinone, was prepared according to the method of Example 228, starting with 2-(3-chlorophenyl)-4-methoxy-5-[3-methyl-4-(methylthio)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)-phenyl]-3(2H)-pyridazinone and substituting 4-fluorophenyl magnesium bromide in place of cyclohexylmagnesium chloride (yield: 180 mg, 94%). ^{1}H NMR (300 MHz,

$CDCl_3$) δ 2.25 (s, 3H), 2.56 (s, 3H), 7.28-7.45 (m, 6H), 7.58-7.63 (m, 1H), 7.71-7.74 (m, 1H), 7.82 (s, 1H). MS (APCI+) m/z 343 $(M+H)^+$ and m/z 360 $(M+NH_4)^+$.

207E. 2-(3-Chlorophenyl)-4-methyl-5-[4-(methylsulfonylphenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 10, substituting 2-(3-chlorophenyl)-4-methyl-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone for 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (yield: 125 mg, 67%). M.p. 164-168. ^1H NMR (300 MHz, $CDCl_3$) δ 2.23 (s, 3H), 3.13 (s, 3H), 7.37-7.46 (m, 2H), 7.61 (m, 3H), 7.71-7.74 (m, 1H), 7.81 (s, 1H), 8.13 (d, J = 8.7 Hz, 2H). MS (APCI+) m/z 343 $(M+H)^+$ and m/z 360 $(M+NH_4)^+$.

207F. 2-(3-Chlorophenyl)-4-bromomethyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(3-Chlorophenyl)-4-bromomethyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone was prepared according to the method of Example 194F, substituting 2-(3-chlorophenyl)-4-methyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-methyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 90 mg, 99%). ^1H NMR (300 MHz, $CDCl_3$) δ 3.13 (s, 3H), 4.33 (s, 2H), 7.40-7.47 (m, 2H), 7.66 (ddd, J = 2.4, 2.4, 7.2 Hz, 1H), 7.76-7.78 (m, 1H), 7.81 (d, J = 8.7 Hz, 2H), 7.86 (s, 1H), 8.17 (d, J = 8.7 Hz, 2H). MS (APCI+) m/z 453 $(M+H)^+$ and m/z 470 $(M+NH_4)^+$.

207G. 2-(3-Chlorophenyl)-4-(4-fluorophenoxymethyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 194G, substituting 2-(3-chlorophenyl)-4-bromomethyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-bromomethyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 30 mg, 31%). M.p. 50-80 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.11 (s, 3H), 4.94 (s, 2H), 6.78-6.85 (m, 2H), 6.91-6.99 (m, 2H), 7.39-7.48 (m, 2H), 7.64 (ddd, J = 7.5, 1.9, 1.9 Hz, 1H), 7.71-7.77 (m, 3H), 7.93 (s, 1H), 8.08 (d, J = 8.7 Hz, 2H). MS (APCI+) m/z 485 $(M+H)^+$.

Example 208

2-(3-Chlorophenyl)-4-(benzoyloxymethyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 207 substituting benzoic acid in place of 4-fluorophenol (yield: 33 mg, 34%). M.p. 50-70

°C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.00 (s, 3H), 5.36 (s, 2H), 7.36-7.48 (m, 4H), 7.52-7.59 (m, 1H), 7.61-7.68 (m, 3H), 7.75-7.78 (m, 1H), 7.83-7.88 (m, 2H), 7.89 (s, 1H), 8.02 (d, J = 8.7 Hz, 2H). MS (APCI+) m/z 495 $(M+H)^+$.

Example 209

2-(2,2,2-Trifluoroethyl)-4-(3-methylbutyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 193 , substituting 1-bromo-4-methylpentane in place of 4-fluorobenzyl bromide (yield: 80 mg, 19%). ^1H NMR (300 MHz, $CDCl_3$) δ 0.81 (d, J = 7.5 Hz, 6H), 1.3-1.6 (m, 3H), 2.52 (m, 2H), 3.14 (3 H, s) 4.85 (q, J = 9 Hz, 2H), 7.55 (d, J = 9 Hz, 2H) 7.67 (s, 1H), 8.1 (d, J = 9 Hz, 2H). MS (DCI-NH_3), m/z 403 $(M+H)^+$. Anal. calc. for $C_{18}H_{21}F_3N_2O_3S \cdot 0.25\ H_2O$: C, 53.12; H, 5.32; N, 6.88. Found C, 52.90; H, 5.14; N, 6.43.

Example 210

2-(2,2,2-Trifluoroethyl)-4-(4-fluoro-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

210A. Preparation of boronic acid:

2-Fluorotoluene-5-Bromo (6 g, 31.7 mmol) was dissolved in dry THF (50 mL) and cooled to -78 C under N_2. n-BuLi (14 mL, 2.5M solution in THF) was added slowly using a dry syringe. Cloudiness appeared. The reaction was stirred for 40 minutes at -78 °C. Triisopropyl borate (22 mL, 95 mmol) was slowly added while stirring. The reaction was allowed to warm to room temperature. Stirring continued for an additional 2 hours. A pale yellow, cloudy solution formed. (TLC (1:2 ethyl acetate /hexanes)) indicated disappearance of the starting material. The reaction was quenched by adding 10% aqueous NaOH (200 mL). After stirring for 45 minutes, 10% citric acid solution (300 mL) was added until, pH ~5.0. The product was extracted with ethyl acetate (500 mL). The organic phase was washed with brine and dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure to provide an off white solid (yield: 4.1 g, 84%).

210B. Suzuki Coupling:

The boronic acid (231 mg, 1.5 mmol), prepared in example 210A, 2-(2,2,2-trifluoroethyl)-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (500 mg, 1.36 mmol), tetrakis-(triphenylphosphine)-palladium(0) (47 mg, 0.041 mmol), and CsF (413 mg, 2.72 mmol) were stirred at reflux in DME (20 mL) under N_2 for 5 hours. TLC (1:1 hexanes/ethyl acetate) indicated that all the starting material was

consumed. Volatiles were removed *in vacuo*. The residue was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo*. An off white powder was obtained (yield: 275 mg, 46%). M.p. 88-91 °C; ^1H NMR (300 MHz, $CDCl_3$, a mixture of rotamers) δ 2.2, 2.25 (2d, J = 1.5 Hz, 3H) 3.05, 3.09 (2 s, 3H) 4.78-4.92 (m, 2H) 6.61-6.8 (m, 1H) 6.82-6.98 (m, 1H) 7.35 (d, J = 9 Hz, 1H) 7.78 (d, J = 9 Hz, 1H) 7.86-8.09 (m, 4H). MS (DCI-NH_3), m/z 441 $(M+H)^+$. Anal. calc. for $C_{20}H_{16}F_4N_2O_3S{\cdot}0.5\ H_2O$: C, 53.45; H, 3.81; N, 6.23. Found C, 53.17; H, 3.65; N, 5.88.

Example 211

2-(2,2,2-Trifluoroethyl)-4-(3,5-dichlorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(2,2,2-Trifluoroethyl)-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (150 mg, 0.409 mmol) (Example 193E) was dissolved in anhydrous DME (8 mL) and heated to reflux with 3,5-dimethylbenzeneboronic acid in presence of CsF (150 mg, 0.98 mmol) and tetrakis(triphenylphosphine)-palladium (17.38 mg, 0.015 mmol) for 6 hours. After cooling to room temperature the reaction mixture was diluted with water and extracted with ethyl acetate (100 mL). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo.* The compound was purified on a silica gel column, eluting with 30% ethyl acetate in pentanes, to provide the title compound (yield: 110 mg, 58%). ^1H NMR (300 MHz, $CDCl_3$) δ 3.08 (s, 3H), 4.88 (q, J = 9 Hz, 2H), 7.06 (d, J = 1.5 Hz, 9 Hz, 2H), 7.31 (t, J = 1.5 Hz, 1H), 7.36 (d, J = 9 Hz, 2H), 7.94 (s, 1H), 7.96 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 496 $(M+NH_4)^+$. Anal. calc. for $C_{19}H_{13}Cl_2F_3N_2O_3S$: C, 47.81; H, 2.75; N, 5.87. Found: C, 47.77; H, 2.75; N, 5.65

Example 212

2-(2,2,2-Trifluoroethyl)-4-(3-ethoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 211, substituting 3-ethoxyphenylboronic acid for 3,5-dimethylbenzeneboronic acid (yield: 155 mg, 86%). ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (t, J = 7.5 Hz, 3H), 3.06 (s, 3H), 3.90 (q, J = 7.5 Hz, 2H), 4.88 (q, J = 9 Hz, 2H), 6.65 (d, J = 7.5 Hz, 1H), 6.75 (t, J = 1.5 Hz, 1H), 6.85 (dd, J = 1.5 Hz, 9 Hz, 1H), 7.15 (t, J = 9 Hz, 1H), 7.38 (d, J = 9 Hz, 2H), 7.88 (d, J = 9 Hz, 2H), 7.90 (s, 1H). MS (DCI-NH_3) m/z 470 $(M+NH_4)^+$.

Anal. calc. for $C_{21}H_{19}Cl_2F_3N_2O_4S$: C, 55.75; H, 4.23; N, 6.19. Found: C, 55.62; H, 4.30; N, 5.99

Example 213

2-(2,2,2-Trifluoroethyl)-4-(4-trifluoromethylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 211, substituting 4-(trifluoromethyl)benzeneboronic acid in place of 3,4-dimethylbenzeneboronic acid (yield: 85 mg, 44%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.08 (s, 3H), 4.90 (q, J = 9 Hz, 2H), 7.35 (t, J = 9 Hz, 4H), 7.58 (d, J = 9 Hz, 2H), 7.90 (d, J = 9 Hz, 3H). MS (DCI-NH_3) m/z 494 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{14}F_6N_2O_3S$: C, 50.42; H, 2.96; N, 5.88. Found: C, 50.20; H, 3.02; N, 5.70

Example 214

2-(2,2,2-Trifluoroethyl)-4-(3-nitrophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 211, substituting 3-nitrobenzeneboronic acid in place of 3,4-dimethylbenzeneboronic acid (yield: 40 mg, 22%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.05 (s, 3H), 4.92 (q, J = 9 Hz, 2H), 7.36 (d, J = 9 Hz, 2H), 7.45-7.60 (m, 2H), 7.91 (d, J = 9 Hz, 2H), 7.95 (s, 1H), 8.05 (m, 1H), 8.15-8.21 (m, 1H). MS (DCI-NH_3) m/z 471 $(M+NH_4)^+$. Anal. calc. for $C_{19}H_{14}Cl_2F_3N_3O_5S \cdot 0.5$ EtOAc: C, 50.70; H, 3.64; N, 8.44. Found: C, 50.61; H, 3.58; N, 8.53

Example 215

2-(2,2,2-Trifluoroethyl)-4-(2-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 211, substituting 2-methylbenzeneboronic acid in place of 3,4-dimethylbenzeneboronic acid (yield: 45 mg, 27%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.05, 2.12 (2s, 3H), 3.01 (s, 3H), 4.75-5.05 (m, 2H), 6.88 (d, J = 9 Hz, 1H), 7.03-7.25 (m, 3H), 7.31 (d, J = 9 Hz, 2H), 7.85 (d, J = 9 Hz, 2H), 7.95 (s, 1H). MS (DCI-NH_3) m/z 440 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{17}F_3N_2O_3S$: C, 55.10; H, 4.27; N, 6.42. Found: C, 55.17; H, 4.18; N, 6.10

Exampl 216

2-(2,2,2-Trifluoroethyl)-4-(4-vinylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 211, substituting 4-vinylbenzeneboronic acid in place of 3,4-dimethylbenzeneboronic acid (yield: 56 mg, 32%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.06, 3.08 (2s, 3H), 4.78-4.95 (m, 2H), 5.30 (t, J = 6 Hz, 1H), 5.65, 5.75(2d, J = 18 Hz, 1H), 6.58-6.92 (m, 1H), 7.1-7.4 (m, 6H), 7.75-8.08 (m, 3H). MS (DCI-NH_3) m/z 452 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{17}F_3N_2O_3S$: C, 58.06; H, 3.94; N, 6.45. Found: C, 57.82; H, 4.01; N, 6.09

Example 217

2-(2,2,2-Trifluoroethyl)-4-[3-(trifluoromethyl)phenyl]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 211, substituting 3-trifluoromethylbenzeneboronic acid in place of 3,4-dimethylbenzeneboronic acid (yield: 120 mg, 63%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.03, 3.08 (2s, 3H), 4.75-4.98 (m, 2H), 7.30-7.60 (m, 6H), 7.75-8.10 (m, 3H). MS (DCI-NH_3) m/z 494 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{14}F_6N_2O_3S$: C, 50.42; H, 2.96; N, 5.88. Found: C, 50.38; H, 2.97; N, 5.74

Example 218

2-(2,2,2-Trifluoroethyl)-4-(3-fluoro-4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 211, substituting 3-fluoro-4-methoxybenzeneboronic acid in place of 3,4-dimethylbenzeneboronic acid (yield: 32 mg, 18%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.05, 3.09 (2s, 3H), 3.85, 3.87 (2s, 3H), 4.78-4.90 (m, 2H), 6.60-7.10 (m, 3H), 7.30-8.15 (m, 5H). MS (DCI-NH_3) m/z 474 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{16}F_4N_2O_4S \cdot 0.5\ H_2O$: C, 51.61; H, 3.68; N, 6.01. Found: C, 51.52; H, 3.65; N, 5.93

Example 219

2-(2,2,2-Trifluoroethyl)-4-(3-fluoro-4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 211 substituting 3-fluoro-4-methylbenzeneboronic acid in place of 3,4-dimethylbenzeneboronic acid (yield: 58 mg, 33%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21, 2.25

(2d, J = 1.5 Hz, 3H), 3.50, 3.55 (2s, 3H), 4.75-4.95 (m, 2H), 6.56-7.15 (m, 3H), 7.30-8.10 (m, 5H). MS (DCI-NH_3) m/z 458 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{16}F_4N_2O_3S{\cdot}0.5\ H_2O$: C, 53.45; H, 3.81; N, 6.23. Found: C, 53.14; H, 3.80; N, 5.97

Example 220

2-(2,2,2-Trifluoroethyl)-4-(3,5-difluoro-4-methoxyphenyl)-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 211, substituting 3,5-difluoro-4-methoxybenzeneboronic acid in place of 3,4-dimethylbenzeneboronic acid. ^1H NMR (300 MHz, $CDCl_3$) δ 2.9, 3.1 (2s, 3H), 3.92, 4.01 (2s, 3H), 4.78-4.95 (m, 2H), 6.25-6.80 (m, 1H), 7.30-7.5 (m, 2H), 7.7-8.15 (m, 4H). MS (DCI-NH_3) m/z 492 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{15}F_5N_2O_4S$: C, 50.64; H, 3.19; N, 5.90. Found: C, 50.542; H, 3.41; N, 5.67

Example 221

2-(2,2,2-Trifluoroethyl)-4-(1,3-dihydro-1-oxo-5-isobenzofuranyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

6-Bromophthalide (300 mg, 1.40 mmol, Teppema et al *Recl. Trav. Chim. Pays-Bays* ,**1923**, *42*, 47) and hexamethylditin (326 µL, 1.55 mmol) were dissolved in toluene (5 mL), degassed with a nitrogen stream for 5 minutes, treated with $(Ph_3P)_4Pd$ (79 mg) and heated at reflux for 1 hour. The reaction was cooled and directly purified by chromatography on a Biotage 40S column (pretreated with hexanes-TEA 400:1 then rinsed with hexanes) eluted with 4:1 hexanes-ethyl acetate. The product fractions were combined and evaporated to provide the intermediate, 6-(trimethyltin)phthalide (yield: 362 mg, 87%).

The tin reagent (180 mg, 0.61 mmol), prepared above, and 2-(2,2,2-trifluoroethyl)-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, prepared in Example 193E, (223 mg, 0.61 mmol) were dissolved in dry toluene (10 mL), degassed with an nitrogen stream for 5 minutes, treated with $(Ph_3P)_4Pd$ (34 mg) and heated at reflux for 1 day. The reaction was cooled and directly purified by chromatography on a Biotage 40S column eluted with 4:1 hexanes-ethyl acetate. The product fractions were combined and evaporated to provide the title compound along with the 4-(1,3-dihydro-1-oxo-6-isobenzofuranyl)-isomer in a 9:1 ratio. Further manipulations to attempt to remove the minor isomer (ie chromatography, recrystallization from ethyl acetate-hexanes) failed (yield: 176 mg, 62%). M.p. 237-

239 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.07 (s, 3H), 4.91 (q, J = 8 Hz, 2H), 5.30 (s, 2 H, major isomer), 5.33 (s, 2 H, minor isomer), 7.20 (dd, J = 1 Hz, 7 Hz, 1H), 7.36 (d, J = 8 Hz, 2H), 7.52 (s, 1H), 7.79 (d, J = 7 Hz, 1H), 7.92 (d, J = 8 Hz, 2H), 7.96 (s, 1H). MS (DCI-NH_3) m/z 482 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{15}F_3N_2O_5S$: C, 54.31; H, 3.26; N, 6.03. Found: C, 54.15; H, 3.12; N, 5.76.

Example 222

2-(2,2,2-Trifluoroethyl)-4-(2-propenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A suspension of 2-(2,2,2-trifluoroethyl)-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (200 mg, 0.546 mmol), prepared according to the method of Example 193E, in THF (27 mL) was cooled to -78 °C. A solution of isopropenyl-magnesium bromide (2.8 mL, 0.5 M in THF, Aldrich) was added. The reaction was warmed to room temperature and stirred for 30 minutes. The reaction was quenched at 0 °C by the addition of saturated ammonium chloride solution and partitioned between ethyl acetate and additional ammonium chloride solution. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide a reddish brown solid. The crude material was dissolved in methylene chloride and adsorbed onto silica gel (2 g). Solvent was removed under reduced pressure, the adsorbed silica gel layered over an Extract-Clean Cartridge® (Alltech, packing: 5 g silica gel) and the cartridge eluted with a hexanes/acetone step gradient consisting of 40 mL of the following mixtures: hexanes, 8:1 hexanes/acetone, 4:1, 2:1, and 1:1. Fractions containing desired product were combined, concentrated, and further purified using HPLC (Technikrom Kromasil 60-5sil column, 20 mm x 25 cm). The column was eluted with a linear gradient consisting of 30% ethyl acetate/hexanes to 100% ethyl acetate at 10 mL/min over 50 minutes. Fractions containing the title product were combined and concentrated under reduced pressure to provide a pale yellow solid (yield: 99.3 mg, 49%). M.p. 192-195 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 17.4 Hz, 2H), 7.76 (s, 1H), 7.55 (d, 2H, J = 17.4 Hz), 5.23 (br s, 1H), 4.84 (m, 3H), 3.11 (s, 3H), 1.98 (s, 3H). MS (DCI-NH_3) m/z 373 $(M+H)^+$, m/z 390 $(M+NH_4)^+$. Anal. calc. for $C_{16}H_{15}F_3N_2O_3S$: C, 51.61; H, 4.06; N, 7.52. Found: C, 51.72; H, 4.24; N, 7.35.

Example 223

2-(2,2,2-Trifluoroethyl)-4-(2-buten-2-yl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 222 substituting 1-methyl-1-propenylmagnesium bromide in place of isopropenylmagnesium bromide to provide a mixture of geometric isomers (~3:1 ratio) as an off-white solid (yield: 44.8 mg, 21%). M.p. 175-180 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 18.0 Hz, 1.5H), 8.01 (d, J = 18.0 Hz, 0.5H), 7.29 (s, 0.75H), 7.28 (s, 0.25H), 7.56 (d, J = 17.4 Hz, 1.5H), 7.51 (d, J = 17.4 Hz, 0.5H), 5.55 (m, 0.75H), 5.33 (m, 0.25H), 5.86 (q, J = 17.4 Hz, 2H), 3.12 (s, 2.25H), 3.11 (s, 0.75H), 2.88 (m, 2H), 2.85 (m, 1H), 1.27 (m, 3H). MS (DCI-NH_3) m/z 387 $(M+H)^+$, m/z 404 $(M+NH_4)^+$, m/z 421 $(M+2NH_4-H)^+$. Anal. calc. for $C_{17}H_{17}F_3N_2O_3S$: C, 52.85; H, 4.43; N, 7.25. Found: C, 53.16; H, 4.68; N, 6.92.

Example 224

2-(2,2,2-Trifluoroethyl)-4-(3-fluorobenzyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

224A. 3-Fluorobenzyl magnesium bromide.

3-Fluorobenzyl bromide (613 µL, 5 mmol), followed by dibromoethane (10 µL), was added dropwise to an oven-dried flask containing small pieces of magnesium ribbon (134 mg, 5.5 mmol) and diethyl ether (12 mL). Gas evolution was noted followed by gentle reflux of the ether. The reaction was stirred until gas evolution ceased and most of the magnesium had dissolved. The resulting pale yellow solution of 3-fluorobenzylmagnesium bromide was used directly in the next reaction.

224B. 2-(2,2,2-Trifluoroethyl)-4-(3-fluorobenzyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

A suspension of 2-(2,2,2-trifluoroethyl)-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (200 mg, 0.546 mmol), prepared according to the method of Example 193E, in THF (10 mL) was cooled to 0 °C. A solution of 3-fluorobenzyl magnesium bromide (4.0 mL, ~0.42 M in diethyl ether), prepared above was added. The reaction was stirred at 0 °C for 3 hours, quenched by the addition of saturated ammonium chloride solution, and partitioned, between ethyl acetate and additional ammonium chloride solution. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide a yellow oil. The crude material was dissolved in methylene chloride and

adsorbed onto silica gel (2 g). Solvent was removed under reduced pressure, the silica gel with the product adsorbed was layered over an Extract-Clean Cartridge® (Alltech, packing: 10 g silica gel) and the cartridge eluted with a hexanes/acetone step gradient consisting of 60 mL of each of the following mixtures: hexanes, 8:1 hexanes/acetone, 4:1, 2:1, and 1:1. Fractions containing desired product were combined, concentrated, and further purified using HPLC (Technikrom Kromasil 60-5 sil silica column, 20 mm x 25 cm). The column was eluted with a linear gradient consisting of 30% ethyl acetate/hexanes to 100% ethyl acetate at 10 mL/min. for 50 minutes. Fractions containing the title product were combined and concentrated under reduced pressure to provide a pale yellow solid (yield: 130.9 mg, 54%). M.p. 58-62 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J = 18.0 Hz, 2H), 7.73 (s, 1H), 7.47 (d, J = 17.4 Hz, 2H), 7.18 (m, 1H), 6.88 (m, 1H), 6.76 (br d, J = 15.6 Hz, 1H), 6.68 (br d, J = 18.6 Hz, 1H), 4.86 (q, J = 17.4 Hz, 2H), 3.93 (s, 2H), 3.12 (s, 3H). MS (DCI-NH_3) m/z 441 $(M+H)^+$, m/z 458 $(M+NH_4)^+$, m/z 475 $(M+2NH_4-H)^+$. Anal. calc. for $C_{20}H_{16}F_4N_2O_3S$: C, 54.54; H, 3.66; N, 6.36. Found: C, 54.52; H, 3.81; N, 6.17.

Example 225

2-(2,2,2-Trifluoroethyl)-4-(1-cyclohexenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

225A. 1-Cyclohexenyltriflate.

n-Butyllithium (2.5M in hexanes, 2.20 mL, 5.50 mmol) was added to a solution of diisopropylamine (0.77 mL, 5.50 mmol) in THF (20 mL) at-78 °C. The resulting pale yellow solution was warmed to 0 °C for 30 minutes then was cooled to -78 °C. Cyclohexanone (0.52 mL, 5.0 mmol) was added and the nearly colorless solution was warmed to 0 °C for 1 hour. N-Phenyltrifluoromethanesulfonimide (1.79 g, 5.5 mmol) was added as a solid. The solution was stirred at room temperature for 12 hours. The reaction mixture was then partitioned between diethyl ether and saturated sodium bicarbonate solution. The ether layer was washed with water then brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (20:1 hexanes/ethyl acetate) to provide the triflate as a pale yellow oil (yield: 0.73 g, 64%).

225B. 1-Cyclohexenyltrimethyltin.

A solution of 1-cyclohexenyltriflate (412 mg, 1.79 mmol), prepared according to the method of Example 225A, and LiCl (380 mg, 8.95 mmol) in THF (9 mL) was

deoxygenated by bubbling a stream of N2 through the solution. Hexamethylditin (339 µL, 1.61 mmol) and tetrakis(triphenylphosphine)palladium(0) (414 mg, 0.36 mmol) were added and the reaction heated at reflux for 12 hours. The reaction was cooled to room temperature and partitioned between diethyl ether and saturated sodium bicarbonate solution. The ether layer was washed with water then brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was dissolved in hexanes (1 mL) and loaded onto an Extract-Clean Cartridge® (Alltech, packing: 10 g silica gel) which had been wetted with 10% triethylamine in hexanes. The cartridge was eluted with hexanes and fractions containing the triflate combined and concentrated under reduced pressure to provide 1-cyclohexenyltrimethyltin as a clear oil (yield: 150 mg, 34%).

225C. <u>2-(2,2,2-Trifluoroethyl)-4-(1-cyclohexenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.</u>

A solution of 1-cyclohexenyltrimethyltin (150 mg, 0.61 mmol), prepared according to the method of Example 225B, and 2-(2,2,2-trifluoroethyl)-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (172 mg, 0.47 mmol), prepared according to the method of Example 193E, in anhydrous N-methylpyrrolidinone (1 mL) was deoxygenated with nitrogen. Dichlorobis(triphenylphosphine) palladium(II) (6.6 mg, 0.009 mmol) and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (7.7 mg, 0.009 mmol) were added and the reaction heated at 80 °C for 16 hours. The reaction mixture was cooled to room temperature and partitioned between diethyl ether and water. The ether was washed with two additional portions water then brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was dissolved in acetone and adsorbed onto silica gel (1 g). Solvent was removed under reduced pressure, the adsorbed silica gel layered over an Extract-Clean Cartridge® (Alltech, packing: 10 g silica gel) and the cartridge eluted with a hexanes/acetone step gradient consisting of the following mixtures: hexanes (60 mL), 8:1 hexanes/acetone (80 mL), 4:1 hexanes/acetone (150 mL). Fractions containing desired product were combined, concentrated, and further purified using HPLC (Technikrom Kromasil 60-5 sil silica column, 20 mm x 25 cm). The column was eluted with a linear gradient consisting of 30% ethyl acetate/hexanes to 100% ethyl acetate at 10 mL/min. over 50 minutes. Fractions containing the title product were combined and concentrated under reduced pressure to provide a pale yellow foam (yield: 95.0 mg, 49%). M.p. 75-81 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 17.4 Hz, 2H), 7.76 (s, 1H), 7.55 (d, J = 17.4 Hz, 2H), 5.51 (br s, 1H), 4.83 (br q, J =

16.2 Hz, 3H), 3.11 (s, 3H), 2.18 (br, 2H), 1.96 (br, 2H), 1.70-1.50 (m, 4H). MS (DCI-NH_3) m/z 413 $(M+H)^+$, m/z 430 $(M+NH_4)^+$, m/z 447 $(M+2NH_4-H)^+$. Anal. calc. for $C_{19}H_{19}F_3N_2O_3S$: C, 55.33; H, 4.64; N, 6.79. Found: C, 55.53; H, 4.71; N, 6.55.

Example 226

2-(2,2,2-Trifluoroethyl)-4-(3-methylbutyl)-5-[3-fluoro-4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

226A. 3-Fluoro-4-(methylthio)benzeneboronic acid.

3-Fluoro-4-(methylthio)benzeneboronic acid was prepared according to the method of Example1, substituting 4-bromo-3-fluorothioanisole in place of 4-bromo-thioanisole.

226B. 2-Benzyl-4-methoxy-5-bromo-3(2H)-pyridazinone

2-Benzyl-4-methoxy-5-bromo-3(2H)-pyridazinone is prepared according to the method of Example 83B starting with 2-benzyl-4,5-dibromo-3(2H)-pyridazinone, in place of 2-(2,2,2-trifluoroethyl)-4,5-dibromo-3(2H)-pyridazinone and substituting methanol in place of isopropanol.

226C. 2-Benzyl-4-methoxy-5-[3-fluoro-4-(methylthio)phenyl]-3(2H)-pyridazinone

3-Fluoro-4-(methylthio)benzeneboronic acid and 2-benzyl-4-methoxy-5-bromo-3(2H)-pyridazinone were coupled according to the method of Example 83C to provide 2-benzyl-4-methoxy-5-[3-fluoro-4-(methylthio)phenyl]-3(2H)-pyridazinone as a yellow solid (yield: 4.98 g, 91%). ^1H NMR (300 MHz, CDCl3) ∂ 7.76 (s, 1H), 7.47 (m, 2H), 7.39-7.21 (m, 7H), 5.34 (s, 2H), 4.13 (s, 3H), 2.51 (s, 3H). MS (DCI-NH3) m/z 357 $(M+H)^+$, m/z 374 $(M+NH4)^+$.

226D. 3-Methylbutylmagnesium bromide

An oven-dried flask containing small pieces of magnesium ribbon (134 mg, 5.5 mmol) was charged with diethyl ether (12 mL). 1-Bromo-3-methylbutane (600 µL, 5 mmol) was added dropwise, followed by dibromoethane (10 µL). The reaction required heating at gentle reflux before gas evolution was observed. The reaction was refluxed for 3 hours and cooled to room temperature. The pale gray solution of 3-methylbutylmagnesium bromide was used in the next reaction.

226E. 2-Benzyl-4-(3-methylbutyl)-5-[3-fluoro-4-(methylthio)phenyl]-3(2H)-pyridazinone

A solution of 2-benzyl-4-methoxy-5-[3-fluoro-4-(methylthio)phenyl]-3(2H)-pyridazinone (500 mg, 1.40 mmol), prepared according to the method of Example 226C, in THF (20 mL) was cooled to-78 °C. 3-Methylbutylmagnesium bromide (5

mL, 1.96 mmol), prepared in Example 226D, was added, dropwise. Upon completion of the addition, the reaction mixture was placed in an ice bath. After 2.5 hours, the reaction was quenched by adding saturated ammonium chloride solution. The crude reaction mixture was partitioned between ethyl acetate and additional ammonium chloride solution. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide a yellow oil (yield: 550 mg, 99%). ^{1}H NMR (300 MHz, CDCl3) ∂ 7.67 (s, 1H), 7.49 (m, 2H), 7.39-7.25 (m, 4H), 7.02 (m, 2H), 5.35 (s, 2H), 2.57-2.49 (m, 2H), 2.52 (s, 3H), 1.62-1.36 (m, 3H), 0.83 (d, 6H, J = 12.0 Hz). MS (DCI-NH3) m/z 397 (M+H)$^+$, m/z 414 (M+NH4)$^+$. MS (DCI-NH_3) m/z 397 (M+H)$^+$, m/z 414 (M+NH_4)$^+$.

226F. <u>4-(3-Methylbutyl)-5-[3-fluoro-4-(methylthio)phenyl]-3(2H)-pyridazinone.</u>

2-Benzyl-4-(3-methylbutyl)-5-[3-fluoro-4-(methylthio)phenyl]-3(2H)-pyridazinone (550 mg, 1.39 mmol), prepared in Example 226E, was debenzylated according to the method of Example 11 to provide 4-(3-methylbutyl)-5-[3-fluoro-4-(methylthio)phenyl]-3(2H)-pyridazinone as a pale yellow solid (yield: 375 mg, 88%). ^{1}H NMR (300 MHz, CDCl3) δ 7.65 (s, 1H), 7.34 (dd, 1H, J = 16.2, 16.2 Hz), 7.11-6.98 (m, 2H), 2.60-2.50 (m, 2H), 2.54 (s, 3H), 1.65-1.37 (m, 3H), 0.83 (d, 6H, J = 12.0 Hz). MS (DCI-NH3) m/z 307 (M+H)$^+$, m/z 324 (M+NH4)$^+$ MS (DCI-NH_3) m/z 307 (M+H)$^+$, m/z 324 (M+NH_4)$^+$.

226G. <u>2-(2,2,2-Trifluoroethyl)-4-(3-methylbutyl)-5-[3-fluoro-4-(methylthio)phenyl]-3(2H)-pyridazinone.</u>

4-(3-Methylbutyl)-5-[3-fluoro-4-(methylthio)phenyl]-3(2H)-pyridazinone (375 mg, 1.23 mmol), prepared in Example 226F, was alkylated according to the method of Example 20 to provide 2-(2,2,2-trifluoroethyl)-4-(3-methylbutyl)-5-[3-fluoro-4-(methylthio)phenyl]-3(2H)-pyridazinone as a clear oil (yield: 331 mg, 69%). ^{1}H NMR (300 MHz, CDCl3) δ 7.67 (s, 1H), 7.34 (dd, 1H, J = 16.8, 16.8 Hz), 7.11-6.98 (m, 2H), 4.82 (dd, 2H, J = 17.4, 17.4 Hz), 2.60-2.51 (m, 2H), 2.53 (s, 3H), 1.61-1.32 (m, 3H), 0.85 (d, 6H, J = 12.0 Hz). MS (DCI-NH3) m/z 389 (M+H)$^+$, m/z 406 (M+NH4)$^+$. MS (DCI-NH_3) m/z 389 (M+H)$^+$, m/z 406 (M+NH_4)$^+$.

226H. <u>2-(2,2,2-Trifluoroethyl)-4-(3-methylbutyl)-5-[3-fluoro-4-(methylsulfinyl)-phenyl]-3(2H)-pyridazinone.</u>

2-(2,2,2-Trifluoroethyl)-4-(3-methylbutyl)-5-[3-fluoro-4-(methylthio)phenyl]-3(2H)-pyridazinone (331 mg, 0.85 mmol), prepared in Example 226G, was oxidized according to the method of Example 5 using only one equivalent of MCPBA to provide 2-(2,2,2-trifluoroethyl)-4-(3-methylbutyl)-5-[3-fluoro-4-(methylsulfinyl)-phenyl]-3(2H)-pyridazinone as an off-white solid (yield: 240 mg, 69%). ^{1}H NMR

(300 MHz, CDCl3) δ 8.02 (dd, 1H, J = 15.0, 15.0 Hz), 7.67 (s, 1H), 7.37 (dd, 1H, J = 17.4, 3.0 Hz), 7.11 (dd, 1H, J = 18.6, 3.0 Hz), 4.84 (dd, 2H, J = 17.4, 17.4 Hz), 2.91 (s, 3H), 2.53 (m, 2H), 1.60-1.35 (m, 3H), 0.57 (d, 6H, J = 12.0 Hz). MS (DCI-NH3) m/z 405 $(M+H)^+$, m/z 422 $(M+NH4)^+$. MS (DCI-NH_3) m/z 405 $(M+H)^+$, m/z 422 $(M+NH_4)^+$.

226I. <u>2-(2,2,2-Trifluoroethyl)-4-(3-methylbutyl)-5-[3-fluoro-4-(aminosulfonyl)-phenyl]-3(2H)-pyridazinone</u>

2-(2,2,2-Trifluoroethyl)-4-(3-methylbutyl)-5-[3-fluoro-4-(methylsulfinyl)-phenyl]-3(2H)-pyridazinone (240 mg, 0.594 mmol), prepared in Example 226H, was converted to the sulfonamide according to the procedure of Example 68 to provide the title compound as a white solid (yield: 109 mg, 44%). M.p. 153-156 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (dd, J = 15.0, 15.0 Hz, 1H), 7.74 (s, 1H), 7.27-7.19 (m, 2H), 5.14 (br s, 2H), 4.83 (q, J = 18.0 Hz, 2H), 2.52 (m, 2H), 1.55 (m, 1H), 1.41 (m, 2H), 0.85 (d, J = 12.6 Hz, 6H). MS (ESI (-)) m/z 420 $(M-H)^-$. Anal. calc. for $C_{17}H_{19}F_4N_3O_3S$: C, 48.45; H, 4.54; N, 9.97. Found: C, 48.24; H, 4.56; N, 9.80.

Example 227

<u>2-(2,2,2-Trifluoroethyl)-4-benzyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone</u>

The title compound was prepared by adding 1.0 M benzylmagnesium chloride in ether (0.53 mL, 0.53 mmol) to a THF (20 mL) solution of 2-(2,2,2-trifluoroethyl)-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (150 mg, 0.41 mmol), prepared according to the method of Example 193E, at 0 °C, then allowing the mixture to warm to room temperature over 2 hours. After an aqueous work-up, the crude material was purified by column chromatography (silica gel, 65:35 hexanes/ethyl acetate) and crystallized from ethyl acetate/hexanes to provide white, crystalline product (yield: 74 mg, 43%). M.p. 112-114 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.12 (s, 3H), 3.94 (s, 2H), 4.85 (q, J = 12 Hz, 2H), 6.99 (dd, J = 7.5 Hz, 3 Hz, 2H), 7.2 (m, 3H), 7.48 (d, J = 9 Hz, 2H), 7.72 (s, 1H), 8.06 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 423 $(M+H)^+$. Anal. calc. for $C_{20}H_{17}F_3N_2O_3S$: C, 56.86; H, 4.05; N, 6.63. Found: C, 56.60; H, 4.13; N, 6.57.

Example 228

<u>2-(4-Fluorophenyl)-4-cyclohexyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone</u>

A solution of 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone, prepared in Example 194C, (200 mg, 0.51 mmol) in THF (8 ml) was cooled to -78 °C and treated with cyclohexylmagnesium chloride, 2 M solution in

ether (0.31 ml, 0,7 mmol). The reaction mixture was stirred at -78 °C for 2 hours and then was warmed up to room temperature by removing the cooling bath. Stirred at room temperature for 2 hours water (50 ml) was added to the reaction mixture and extracted with ethyl acetate (50 ml). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The resulting methyl sulfide compound was purified by flash chromatography (SiO_2, eluting with 9:1 hexanes:ethyl acetate) to provide the desired product (yield: 128 mg, 69%). MS (DCI-NH_3) m/z 395 $(M+H)^+$, 412 $(M+NH_4)^+$.

The methyl sulfide compound, prepared above, (122 mg, 0.3 mmol) in CH_2Cl_2 (10 ml) at 0 °C, was treated with CH_3CO_3H (0.3 ml, 1 mmol). The reaction was complete in 2 hours. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ and brine respectively. The resulting crude residue was purified by flash chromatography (SiO_2, eluting with 1:1 hexanes:ethyl acetate) to provide the desired product (yield: 110 mg, 93%). M.p. 231-233 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 1.1 (m, 3H), 1.6 (m, 6H), 2.15 (m, 2H), 7.35 (t, 2H), 7.65 (m, 2H), 7.73 (dd, 2H) 7.93 (s, 1H), 8.1 (d, 2H). MS (DCI-NH_3) m/z 427 $(M+H)^+$, 444 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{23}FN_2O_3S \cdot 0.75\ H_2O$: C, 64.77; H, 5.44; N, 6.57. Found: C, 62.86; H, 5.53; N, 5.78.

Example 229

2-(4-Fluorophenyl)-4-(4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228, substituting p-tolylmagnesium bromide in place of cyclohexylmagnesium chloride (yield: 90 mg, 39%). M.p. 242-244 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 2.25 (s, 3H), δ 3.25 (s, 3H), 7.1 (t, 4H), 7.35 (t, 2H), 7.5 (d, J = 9 Hz, 2H), 7.7 (dd, 2H) 7.9 (d, J = 9 Hz, 2H), 8.2 (s, 1H). MS (DCI-NH_3) m/z 435 $(M+H)^+$, 452 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{19}FN_2O_3S \cdot 0.5\ H_2O$: C, 66.34; H, 4.41; N, 6.45. Found: C, 64.61; H, 4.57; N, 6.10.

Example 230

2-(4-Fluorophenyl)-4-benzyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228, substituting benzylmagnesium bromide in place of cyclohexylmagnesium chloride (yield: 179 mg, 81%). M.p. 180-182 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 3.3 (s, 3H), 7.0 (d, 2H), 7.2 (m, 3H), 7.35 (t, 2H), 7.65 (m, 2H)7.72 (d, 2H) 8.05 (m, 3H). MS

(DCI-NH_3) m/z 435 $(M+H)^+$, 452 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{19}FN_2O_3S \cdot 0.5 H_2O$: C, 66.34; H, 4.41; N, 6.45. Found: C, 66.48; H, 4.17; N, 6.36.

Example 231

2-(4-Fluorophenyl)-4-(phenylethynyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228, substituting phenylacetylene magnesium bromide in place of cyclohexylmagnesium chloride (yield: 150 mg, 55.5%). M.p. 203-204 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 3.3 (s, 3H), 7.4 (m, 8H), 7.7 (m, 2H), 8.16 (m, 4H) ; 8.35 (s, 1H). MS (DCI-NH_3) m/z 435 $(M+H)^+$, 452 $(M+NH_4)^+$. Anal. calc. for $C_{25}H_{17}FN_2O_3S$: C, 67.56; H, 3.86; N, 6.30. Found: C, 67.63; H, 3.86; N, 6.30.

Example 232

2-(3,4-Difluorophenyl)-4-cyclohexyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228, starting with 2-(3,4-difluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 245 mg, 80%). M.p. 80-83 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 1.1 (m, 3H), 1.6 (m, 6H), 2.15 (m, 2H), 7.5 (m, 1H), 7.6 (m, 2H), 7.7 (d, 2H), 7.78 (m, 2H), 7.93 (s, 1H), 8.1 (d, 2H). MS (DCI-NH_3) m/z 445 $(M+H)^+$, 462 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{22}F_2N_2O_3S$: C, 62.15; H, 4.99; N, 6.30. Found: C, 62.65; H, 5.25; N, 5.97.

Example 233

2-(3,4-Difluorophenyl)-4-benzyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228, starting with 2-(3,4-difluorophenyl)-4-methoxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(3,4-difluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone and substituting benzylmagnesium bromide in place of cyclohexylmagnesium chloride (yield 206 mg, 66%). M.p. 166-168 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 3.3 (s, 3H), 3.9 (s, 2H), 7.0 (d, 2H), 7.2 (m, 3H), 7.6 (m, 2H), 7.72 (d, 2H), 7.8 (d, 1H), 8.05 (d, 2H), 8.12 (s, 1H). MS (DCI-NH_3) m/z 453 $(M+H)^+$, 470 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{19}F_2N_2O_3S$: C, 63.71; H, 4.01; N, 6.19. Found: C, 63.53; H, 4.33; N, 5.76.

Example 234

2-(3,4-Difluorophenyl)-4-(4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228, starting with 2-(3,4-difluorophenyl)-4-methoxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(3,4-difluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone and substituting cyclohexylmagnesium chloride in place of p-tolylmagnesium bromide (yield: 140 mg, 56%) . M.p. 190-192 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.28 (s, 2H), δ 3.25 (s, 3H), 7.1 (s, 4H), 7.5 (m, 4H), 7.89 (m, 3H), 8.05 (d, 2H), 8.23 (s, 1H). MS (DCI-NH_3) m/z 453 $(M+H)^+$, 470 $(M+NH_4)^+$. Anal. calc. for $C_{24}F_2H_{18}N_2O_3S$: C, 63.71; H, 4.01; N, 6.19. Found: C, 63.69; H, 4.29; N, 5.96.

Example 235

2-(3,4-Difluorophenyl)-4-(4-fluoro-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228, starting with 2-(3,4-difluorophenyl)-4-methoxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone and substituting 4-fluoro-3-methylbenzenemagnesium bromide in place of cyclohexylmagnesium chloride (yield: 180 mg, 72.5%) . M.p. 166-168 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.15 (s, 3H), δ 3.25 (s, 3H), 7.01 (m, 2H), 7.25 (d, 1H), 7.6 (m, 4H), 7.9 (m, 3H), 8.26 (s, 2H). MS (DCI-NH_3) m/z 471 $(M+H)^+$, 488 $(M+NH_4)^+$. Anal. calc. for $C_{24}F_3H_{17}N_2O_3S$: C, 61.27; H, 3.64; N, 5,95. Found: C, 61.47; H, 3.84; N, 5.67.

Example 236

2-(3,4-Difluorophenyl)-5-[4-(methylsulfonyl)phenyl]-4-vinyl-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228, starting with 2-(3,4-difluorophenyl)-4-methoxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone and substituting vinyl magnesium bromide in place of cyclohexylmagnesium chloride (yield: 85 mg, 31.8%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.15 (s, 3H), δ 3.3 (s, 3H), 5.7 (dd, 1H), 6.4 (dd, 1H), 6.7 (dd, 1H) 7.01 (m, 2H),

7.5 (m, 1H), 7.65 (m, 1H), 7.8 (m, 3H), 8.1 (s, 3H). MS (DCI-NH_3) m/z 389 $(M+H)^+$, 406 $(M+NH_4)^+$.

Example 237

2-(3,4-Difluorophenyl)-4-(2-thienyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228, starting with 2-(3,4-difluorophenyl)-4-methoxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone and substituting 2-thienylmagnesium bromide in place of cyclohexylmagnesium chloride (yield: 66 mg, 28%). M.p. 189-191 °C ^1H NMR (300 MHz, DMSO-d_6) δ 3.3 (s, 3H), 6.95 (m, 2H), 7.55 (m, 1H), 7.7 (m, 5H), 7.85 (m, 1H), 8.03 (d, J = 9 Hz, 2H), 8.13 (s, 1H). MS (DCI-NH_3) m/z 445 $(M+H)^+$, 462 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{14}F_2N_2O_3S_2$: C, 56.75; H, 3.17; N, 6.30. Found: C, 56.92, H, 3.92, N, 5.79.

Example 238

2-(3,4-Difluorophenyl)-4-(1-propynyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228, starting with 2-(3,4-difluorophenyl)-4-methoxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone and substituting methylacetylenemagnesium bromide in place of cyclohexylmagnesium chloride (yield: 65 mg, 24%) . M.p. 149-150 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 2.1 (s, 3H), 3.3 (s, 3H), 7.51 (m, 1H), 7.65 (m, 1H), 7.8 (m, 1H), 8.1 (m, 4H) ; 8.3 (s, 1H). MS (DCI-NH_3) m/z 463M+H)$^+$, 480 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{14}F_2N_2O_3S \cdot 0.25$ H2O: C, 59.94; H, 3.52; N, 7.00. Found: C, 59.49; H, 3.63; N, 6.34.

Example 239

2-(3,4-Difluorophenyl)-4-t-butyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228, starting with 2-(3,4-difluorophenyl)-4-methoxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone and substituting t-butylmagnesium bromide in place of cyclohexylmagnesium chloride (yield: 60 mg, 24%). M.p. 158-161 °C. ^1H NMR

(300 MHz, DMSO-d_6) δ 1.21, (s, 9H), 3.3 (s, 3H), 7.51 (m, 1H), 7.45 (m, 1H), 7.75 (m, 4H), 8.02 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 419 $(M+H)^+$, 436 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{20}F_2N_2O_3S$: C, 60.27; H, 4.82; N, 6.69. Found: C, 60.15; H, 5.10; N, 6.39

Example 240

2-(2,2,2-Trifluoroethyl)-4-cyclohexyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228, starting with 2-(2,2,2-trifluoroethyl)-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, prepared in Example 193E, in place of 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone, (yield: 120 mg, 53%). M.p. 215-218 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.1 (tt, J = 9 Hz, J = 4.5 Hz, 2H), 1.25 (tt, J = 9 Hz, 4.5 Hz, 1H), 1.49 (d, J = 12 Hz, 2H), 1.63 (d, J = 12 Hz, 1H), 1.75 (dt, J = 12 Hz, 3 Hz, 2H), 2.21 (qd, J = 9 Hz, 4.5 Hz, 2H), 2.51 (tt, J = 12 Hz, 3 Hz, 1H), 3.17 (s, 3H), 4.83 (q, J = 12 Hz, 2H), 7.49 (d, J = 9 Hz, 2H), 7.6 (s, 1H), 8.09 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 415 $(M+H)^+$. Anal. calc. for $C_{19}H_{21}F_3N_2O_3S$: C, 55.06; H, 5.1; N, 6.75. Found: C, 55.08; H, 5.10; N, 6.70.

Example 241

2-(3-Chlorophenyl)-4-(3-fluorobenzyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(3-Chlorophenyl)-4-(3-fluorobenzyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone was prepared according to the method of Example 228, starting with 2-(3-chlorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone, prepared in Example 331, and substituting 3-fluorobenzylmagnesium chloride in place of cyclohexylmagnesium chloride to provide the methyl sulfide compound.

The methyl sulfide compound was oxidized according to the method of Example 10 to provide the title compound (yield: 180 mg, 55%). M.p. 142-143 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.14 (s, 3H), 3.98 (s, 2H), 6.75 (br d, J = 9 Hz, 1H), 6.82 (br d, J = 9 Hz, 1H), 6.88 (br t, J = 9 Hz, 1H), 7.15-7.23 (m, 1H), 7.37-7.47 (m, 2H), 7.54 (d, J = 9 Hz, 2H), 7.63 (dt, J = 9 Hz, 2 Hz, 1H), 7.75 (t, J = 2 Hz, 1H), 7.82 (s, 1H), 8.10 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 469 $(M+H)^+$, 486 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{18}ClF_2N_2O_3S \cdot 0.5\ H_2O$: C, 60.38; H, 3.88; N, 5.87. Found: C, 60.62; H, 3.89; N, 5.82.

Example 242

2-(4-Fluorophenyl)-4-(3-fluorobenzyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(4-Fluorophenyl)-4-(3-fluorobenzyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone was prepared according to the method of Example 228, starting with 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone, prepared in Example 194C, and substituting 3-fluorobenzylmagnesium chloride in place of cyclohexylmagnesium chloride to provide the methyl sulfide compound.

The methyl sulfide compound was oxidized according to the method of Example 10, to provide the title compound (yield: 450 mg, 66.8%). M.p. 176-178 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.14 (s, 3H), 3.95 (s, 2H), 6.75 (br d, J = 9 Hz, 1H), 6.82 (br d, J = 9 Hz, 1H), 6.88 (br t, J = 9 Hz, 1H), 7.14-7.23 (m, 3H), 7.54 (d, J = 9 Hz, 2H), 7.67 (dd, J = 9 Hz, 6 Hz, 2H), 7.81 (s, 1H), 8.10 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 516 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{19}F_2N_2O_5S{\cdot}H_2O$: C, 61.28; H, 4.04; N, 5.96. Found: C, 61.24; H, 4.09; N, 5.77.

Example 243

2-(3,4-Difluorophenyl)-4-(3-fluorobenzyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(3,4-Difluorophenyl)-4-(3-fluorobenzyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone was prepared according to the method of Example 228, starting with 2-(3,4-difluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone prepared in Example 206E, and substituting 3-fluorobenzylmagnesium chloride in place of cyclohexylmagnesium chloride to provide the methyl sulfide compound.

The methyl sulfide compound was oxidized according to the method of Example 10 to provide the title compound (yield: 390 mg, 68%). M.p. 161-163 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.14 (s, 3H), 3.95 (s, 2H), 6.74 (br d, J = 9 Hz, 1H), 6.82 (br d, J = 9 Hz, 1H), 6.89 (br t, J = 9 Hz, 1H), 7.15-7.33 (m, 2H), 7.48-7.57 (m, 1H), 7.53 (d, J = 9 Hz, 2H), 7.59-7.67 (m, 1H), 7.83 (s, 1H), 8.10 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 471 $(M+H)^+$, 488 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{17}F_3N_2O_3S{\cdot}0.5\ H_2O$: C, 60.13; H, 3.65; N, 5.85. Found: C, 60.08; H, 3.81; N, 5.54.

Example 244

2-(3-Chlorophenyl)-4-(4-fluoro-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(3-Chlorophenyl)-4-(4-fluoro-3-methylphenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone was prepared according to the method of Example 228, starting with 2-(3-chlorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone, prepared in Example 207B, and substituting 4-fluoro-3-methylphenylmagnesium bromide in place of cyclohexylmagnesium chloride to provide the methyl sulfide compound.

The methyl sulfide compound was oxidized according to the method of Example 10 to provide the title compound (yield: 620 mg, 57%). M.p. 228-230 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 3H), 3.06 (s, 3H), 6.83-6.93 (m, 2H), 7.19 (br d, J = 9 Hz, 1H), 7.37-7.47 (m, 2H), 7.40 (d, J = 9 Hz, 2H), 7.65 (dt, J = 7 Hz, 3 Hz, 1H), 7.68 (t, J = 3 Hz, 1H), 7.91 (d, J = 9 Hz, 2H), 7.98 (s, 1H). MS (DCI-NH_3) m/z 469 $(M+H)^+$, 486 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{18}ClFN_2O_3S$: C, 61.54; H, 3.85; N, 5.99. Found: C, 61.39; H, 3.84; N, 5.82.

Example 245

2-(4-Fluorophenyl)-4-(4-fluoro-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(4-Fluorophenyl)-4-(4-fluoro-3-methylphenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone was prepared according to the method of Example 228, starting with 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone, prepared in Example 194C, and substituting 4-fluoro-3-methylphenylmagnesium bromide in place of cyclohexylmagnesium chloride to provide the methyl sulfide compound.

The methyl sulfide compound was oxidized according to the method of Example 10 to provide the title compound (yield: 590 mg, 74.4%). M.p. 245-247 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.01 (s, 3H), 3.07 (s, 3H), 6.87 (m, 2H), 7.21 (m, 3H), 7.41 (d, J = 9 Hz, 2H), 7.68 (m, 2H), 7.92 (d, J = 9 Hz, 2H), 7.97 (s, 1H). MS (DCI-NH_3) m/z 453 $(M+H)^+$, 470 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{18}F_2N_2O_3S \cdot 0.5\ H_2O$: C, 62.47; H, 3.90; N, 6.08. Found: C, 62.11; H, 4.11; N, 5.81.

Example 246

2-(3-Chloro-4-fluorophenyl)-4-cyclohexyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

246A. 2-(3-Chloro-4-fluorophenyl)-4,5-dibromo-3(2H)-pyridazinone.

The title compound is prepared according to the method of Example 194A, substituting 3-chloro-4-fluorophenyl hydrazine·HCl in place of 4-fluorophenyl hydrazine·HCl (yield: 9.1 g, 9%). ^{1}H NMR (300 MHz, $CDCl_3$) 7.22 (d, J = 9 Hz, 1H), 7.53-7.58 (m, 1H), 7.73 (dd, J = 9 Hz, 3 Hz, 1H), 7.94 (s, 1H). MS (DCI-NH_3) m/z 383 $(M+H)^+$, 400 $(M+NH_4)^+$

246B. 2-(3-Chloro-4-fluorophenyl)-4-methoxy-5-bromo-3(2H)-pyridazinone.

The title compound is prepared according to the method of Example 194B, substituting 2-(3-chloro-4-fluorophenyl)-4,5-dibromo-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4,5-dibromo-3(2H)-pyridazinone (yield: 5.6 g, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) 4.32 (s, 3H), 7.22-7.30 (m, 1H), 7.45-7.55 (m, 1H), 7.64-7.74 (m, 1H), 7.94 (d, J = 9 Hz, 1H). MS (DCI-NH_3) m/z 335 $(M+H)^+$, 352 $(M+NH_4)^+$.

246C. 2-(3-Chloro-4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone.

The title compound is prepared according to the method of Example 6 starting with 2-(3-chloro-4-fluorophenyl)-4-methoxy-5-bromo-3(2H)-pyridazinone in place of 2-benzyl-5-methoxy-4-bromo-3(2H)-pyridazinone and substituting 3-methyl-4-(methylthio)benzeneboronic acid in place of 4-fluorobenzeneboronic acid (yield: 3.2 g, 63%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.53 (s, 3H), 4.13 (s, 3H), 7.25 (t, J = 9 Hz, 1H), 7.35 (d, J = 9 Hz, 2H), 7.52 (d, J = 9 Hz, 2H), 7.55-7.64 (m, 1H), 7.78 (dd, J = 9 Hz, 3 Hz, 1H), 7.93 (s, 2H). MS (DCI-NH_3) m/z 377 $(M+H)^+$, 394 $(M+NH_4)^+$.

246D. 2-(3-Chloro-4-fluorophenyl)-4-cyclohexyl-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone

The title compound is prepared starting with 2-(3-chloro-4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone by treatment of the methoxy-sulfide compound with cyclohexylmagnesium chloride according to the method of Example 228 to provide the cyclohexyl sulfide compound.

246E. 2-(3-Chloro-4-fluorophenyl)-4-cyclohexyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

The methyl sulfide compound was oxidized according to the method of Example 10 to provide the title compound (yield: 150 mg, 53%). M.p. 180-181 °C.

^1H NMR (300 MHz, $CDCl_3$) δ 1.02-1.36 (m, 2H), 1.49-1.68 (m, 4H), 1.75 (br d, J = 12 Hz, 2H), 2.28 (dq, J = 12 Hz, 3 Hz, 2H), 2.57 (tt, J = 12 Hz, 3 Hz, 1H), 3.17 (s, 3H), 7.25 (t, J = 9 Hz, 1H), 7.53 (d, J = 9 Hz, 1H), 7.53-7.61 (m, 2H), 7.69 (s, 1H), 7.78 (dd, J = 9 Hz, 3 Hz, 1H), 8.12 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 461 $(M+H)^+$, 478 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{22}ClFN_2O_3S$: C, 60.01; H, 4.78; N, 6.09. Found: C, 59.85; H, 4.97; N, 5.79.

Example 247

2-(3-Chloro-4-fluorophenyl)-4-(4-fluoro-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(3-Chloro-4-fluorophenyl)-4-(4-fluoro-3-methylphenyl)-5-[4-(methylthio)-phenyl]-3(2H)-pyridazinone was prepared according to the method of Example 228, starting with 2-(3-chloro-4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone, prepared in Example 246D, and substituting 4-fluoro-3-methylphenylmagnesium bromide in place of cyclohexylmagnesium chloride to provide the methyl sulfide compound.

The methyl sulfide was oxidized according to the method of Example 10 to provide the title compound (yield: 118 mg, 53.7%). M.p. 207-208 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 2.21 (br s, 3H), 3.08 (s, 3H), 6.81-6.93 (m, 2H), 7.15-7.30 (m, 2H), 7.41 (d, J = 9 Hz, 2H), 7.60-7.68 (m, 1H), 7.85 (dd, J = 9 Hz, 3 Hz, 1H), 7.93 (d, J = 9 Hz, 2H), 7.99 (s, 1H). MS (DCI-NH_3) m/z 487 $(M+H)^+$, 504 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{17}ClF_2N_2O_3S \cdot 0.25\ H_2O$: C, 58.75; H, 3.52; N, 5.72. Found: C, 58.74; H, 3.60; N, 5.32.

Example 248

2-(3-Chloro-4-fluorophenyl)-4-benzyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(3-Chloro-4-fluorophenyl)-4-benzyl-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone was prepared according to the method of Example 228, starting with 2-(3-chloro-4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone, prepared in Example 246D, and substituting benzylmagnesium chloride in place of cyclohexylmagnesium chloride to provide the methyl sulfide compound.

The methyl sulfide was oxidized according to the method of Example 10 to provide the title compound (yield: 110 mg, 38.4%). M.p. 164-166 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.11 (s, 3H), 3.99 (s, 2H), 7.01-7.06 (m, 2H), 7.17-7.28 (m, 4H), 7.53

(d, J = 9 Hz, 2H), 7.59-7.66 (m, 1H), 7.81 (s, 1H), 7.82 (dd, J = 6 Hz, 3 Hz, 1H), 8.09 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 473 $(M+H)^+$, 490 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{18}ClFN_2O_3S$: C, 61.54; H, 3.85; N, 5.99. Found: C, 61.40; H, 3.82; N, 5.54.

Example 249

2-(3-Chloro-4-fluorophenyl)-4-(3-fluorobenzyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(3-Chloro-4-fluorophenyl)-4-(3-fluorobenzyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone was prepared according to the method of Example 228, starting with 2-(3-chloro-4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone, prepared in Example 246D, and substituting 3-fluorobenzyl-magnesium chloride in place of cyclohexylmagnesium chloride to provide the methyl sulfide compound.

The methyl sulfide was oxidized according to the method of Example 10 to provide the title compound (yield: 33 mg, 15%). M.p. 101-103 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.15 (s, 3H), 3.95 (s, 2H), 6.73 (br d, J = 9 Hz, 1H), 6.81 (br d, J = 9 Hz, 1H), 6.88 (br t, J = 9 Hz, 1H), 7.15-7.28 (m, 2H), 7.51 (d, J = 9 Hz, 2H), 7.53 (ddd, J = 9 Hz, 3 Hz, 1.5 Hz, 1H), 7.83 (dd, J = 6 Hz, 3 Hz, 1H), 7.83 (s, 1H), 8.10 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 487 $(M+H)^+$, 504 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{17}ClF_2N_2O_3S$: C, 58.75; H, 3.52; N, 5.62. Found: C, 58.50; H, 3.65; N, 5.29.

Example 250

2-(4-Fluorophenyl)-4-(3-fluoro-4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(4-Fluorophenyl)-4-(3-fluoro-4-methylphenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone was prepared according to the method of Example 228, starting with 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone, prepared in Example 194C, and substituting 3-fluoro-4-methyl-phenylmagnesium bromide in place of cyclohexylmagnesium chloride to provide the methyl sulfide compound.

The methyl sulfide was oxidized according to the method of Example 10 to provide the title compound (yield: 540 mg, 73%). M.p. 245-248 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 2.22 (br s, 3H), 3.05 (s, 3H), 6.83 (dd, J = 9 Hz, 1.5 Hz, 1H), 6.96 (dd, J = 9 Hz, 1.5 Hz, 1H), 7.06 (t, J = 9 Hz, 1H), 7.18 (t, J = 9 Hz, 2H), 7.41 (d, J = 9 Hz, 2H), 7.65-7.72 (m, 2H), 7.91 (d, J = 9 Hz, 2H), 7.95 (s, 1H). MS (DCI-NH_3) m/z

452 (M+H)+, 470 (M+NH4)+. Anal. calc. for $C_{24}H_{18}F_2N_2O_3S$: C, 63.86; H, 3.99; N, 6.21. Found: C, 63.49; H, 4.13; N, 5.98.

Example 251

2-(3-Chloro-4-fluorophenyl)-4-(3,5-difluoro-4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(3-Chloro-4-fluorophenyl)-4-(3,5-difluoro-4-methoxyphenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone was prepared according to the method of Example 228, starting with 2-(3-chloro-4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone, prepared in Example 246D, and substituting 3,5-difluoro-4-methoxyphenylmagnesium bromide in place of cyclohexylmagnesium chloride to provide the methyl sulfide compound.

The methyl sulfide was oxidized according to the method of Example 10 to provide the title compound (yield: 590 mg, 65.7%). M.p. 195-197 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.10 (s, 3H), 4.12 (s, 3H), 6.81 (br d, J = 9 Hz, 2H), 7.27 (t, J = 9 Hz, 1H), 7.43 (d, J = 9 Hz, 2H), 7.60-7.67 (m, 1H), 7.83 (br d, J = 9 Hz, 1H), 7.98 (d, J = 9 Hz, 2H), 7.98 (s, 1H). MS (DCI-NH_3) m/z 487 (M+H)+, 504 (M+NH_4)+. Anal. calc. for $C_{24}H_{16}ClF_3N_2O_3S \cdot 0.5\ H_2O$: C, 54.44; H, 3.12; N, 5.30. Found: C, 54.50; H, 3.12; N, 5.15.

Example 252

2-(3-Chloro-4-fluorophenyl)-4-(3-methylbutyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(3-Chloro-4-fluorophenyl)-4-(3-methylbutyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone was prepared according to the method of Example 228, starting with 2-(3-chloro-4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone, prepared in Example 246D, and substituting 1-(3-methylbutyl)-magnesium bromide in place of cyclohexylmagnesium chloride to provide the methyl sulfide compound.

The methyl sulfide was oxidized according to the method of Example 10 to provide the title compound (yield: 425 mg, 54.4%). M.p. 102-104 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, J = 9 Hz, 6H), 1.41-1.62 (m, 1H), 2.50-2.63 (m, 2H), 3.30 (s, 3H), 7.22-7.38 (m, 3H), 7.57-7.64 (m, 1H), 7.72 (br s, 1H), 7.80 (br d, J = 6 Hz, 1H), 8.15 (t, J = 9 Hz, 1H). MS (DCI-NH_3) m/z 467 (M+H)+, 484 (M+NH_4)+. Anal. calc. for $C_{22}H_{21}ClF_2N_2O_3S$: C, 56.65; H, 4.51; N, 6.01. Found: C, 56.25; H, 4.49; N, 6.06.

Example 253

2-(4-Fluorophenyl)-4-(3-fluorobenzyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The methyl sulfide intermediate from Example 242 was oxidized to the methyl sulfoxide with one equivalent of *meta*-chloroperoxybenzoic acid according to the procedure in Example 69B to provide the sulfinyl compound.

The sulfoxide was converted to the title sulfonamide according to the method of Example 68 (yield: 120 mg, 31%). M.p. 199-202 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.92 (s, 2H), 6.85 (br t, J = 9 Hz, 2H), 6.99 (br t, J = 9 Hz, 1H), 7.26 (q, J = 7 Hz, 1H), 7.35 (t, J = 9 Hz, 2H), 7.50 (s, 2H), 7.62-7.71 (m, 4H), 7.95 (d, J = 9 Hz, 2H), 8.11 (s, 1H). MS (DCI-NH_3) m/z 454 $(M+H)^+$, 471 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{17}F_2N_3O_3S$: C, 60.86; H, 3.75; N, 9.27. Found: C, 60.99; H, 3.76; N, 9.02.

Example 254

2-(3,4-Difluorophenyl)-4-(phenylethynyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 232 substituting phenylethynylmagnesium bromide in place of chloride (yield: 195 mg, 61%). M.p. 211-213 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.46 (m, 5H), 7.65 (m, 2H), 8.18 (t, 4H) ; 8.4 (s, 1H). MS (DCI-NH_3) m/z 463M+H)$^+$, 480 $(M+NH_4)^+$. Anal. calc. for $C_{25}H_{16}F_2N_2O_3S$: C, 64.56; H, 3.49; N, 6.06. Found: C, 64.49; H, 3.68; N, 5.86.

Example 255

2-(3,4-Difluorophenyl)-4-(3,4-difluorobenzyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

3,4-Difluorobenzyl bromide (0.1 ml, 0.8 mmol) in ether (10 ml) was treated with magnesium turnings (19.4 mg, 0.81 mmol) and the reaction mixture was refluxed for 1 hour. The reaction mixture was cooled and added to a solution of 2-(3,4-difluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (0.25 g, 0.7 mmol) in THF (10 ml) at -78 °C. The reaction mixture was stirred at room temperature for 18 hours. Water (50 ml) was added to the reaction mixture and extracted with ethyl acetate (50 ml). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude residue was purified by flash

chromatography (SiO_2, eluting with 9:1 hexanes:ethyl acetate) to provide 120 mg of desired product and some starting material.

The methylthio compound (120 mg, 0.3 mmol) from above in CH_2Cl_2 (10 ml) at 0 °C, was treated with CH_3CO_3H (0.3 ml, 1 mmol). The reaction was complete in 2 hours. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ and brine respectively. The resulting crude residue was purified by flash chromatography (SiO_2, eluting with 1:1 hexanes:ethyl acetate) to provide the desired product (yield: 44 mg, 13%). M.p. 177-179 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 3.3 (s, 3H), 3.9 (s, 2H), 6.85 (m, 1H), 7.15 (m, 1H), 7.25 (m, 2H), 7.6 (m, 7H), 8.15 (m, 3H). MS (DCI-NH_3) m/z 489 $(M+H)^+$, 506 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{16}F_4N_2O_3S \cdot 0.25\ H_2O$: C, 59.01; H, 3.30; N, 5.74. Found: C, 58.16; H, 3.56; N, 4.51.

Example 256

2-(3,4-Difluorophenyl)-4-(3-methylbutyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 233, starting with 2-(3,4-difluorophenyl)-4-methoxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(3,4-difluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone and substituting 1-bromo-3-methylbutane in place of 3,4-difluorobenzyl bromide (yield: 198 mg, 48%). M.p. 55-58 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 0.75 (d, 6H), 1.4, (m, 3H), 2.48 (m, 2H), 3.3 (s, 3H), 7.51 (m, 1H), 7.65 (m, 1H), 7.75 (d, J = 9 Hz, 2H), 7.81 (m, 1H) 8.05 (s, 1H), 8.12 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 433 $(M+H)^+$, 450 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{22}F_2N_2O_3S \cdot 0.25\ H_2O$: C, 61.10; H, 5.13; N, 6.48. Found: C, 61.09; H, 5.23; N, 6.36.

Example 257

2-(3-Chloro-4-fluorophenyl)-4-(3-methylbutyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 233, procedure starting with 2-(3,4-difluorophenyl)-4-methoxy-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone with 2-(3-chloro-4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone and substituting 1-bromo-3-methylbutane in place of 3,4-difluorobenzyl bromide (yield: 256 mg, 88%). M.p. 55-58 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 0.75 (d, 6H), 1.4, (m, 3H), 2.48 (m, 2H), 3.3 (s, 3H),

7.62 (m, 2H), 7.75 (d, 2H), 7.93 (dd, 1H), 8.05 (s, 1H), 8.12 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 449 $(M+H)^+$, 466 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{22}FN_2O_3SCl \cdot 0.25\ H_2O$: C, 58.86; H, 4.94; N, 6.24 . Found: C, 59.23; H, 5.12; N, 6.00.

Example 258

2-(3,4-Difluorophenyl)-4-(3-methylbutyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 233, procedure starting with 2-(3,4-difluorophenyl)-4-methoxy-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone in place of 2-(3-chloro-4-fluorophenyl)-4-methoxy-5-[3-fluoro-4-(methylthio)phenyl]-3(2H)-pyridazinone and substituting 1-bromo-3-methylbutane in place of 3,4-difluorobenzyl bromide (yield: 100 mg, 20%) . M.p. 119-121 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 0.75 (d, 6H), 1.4, (m, 3H), 2.48 (m, 2H), 3.4 (s, 3H), 7.51 (m, 1H), 7.8 (m, 2H), 7.81 (m, 2H). MS (DCI-NH_3) m/z 451 $(M+H)^+$, 468 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{21}F_3N_2O_3S$: C, 58.66; H, 4.7; N, 6.22.

Example 259

2-[4-Fluoro-3-(methylthio)phenyl]-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

To a stirred solution of 2-(3,4-difluorophenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (315 mg, 0.69 mmol) in DMF (10 ml) at room temperature was treated with sodium thiomethoxide (51 mg, 0.7 mmol). The reaction mixture was stirred at room temperature for 3.15 hours. The reaction was poured into water (75 ml) and extracted into ethyl acetate. The organic layer was washed two times with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The resulting crude residue was purified using flash chromatography (SiO_2, eluting with (15:1 CH_2Cl_2:diethyl ether) to provide the desired product (yield: 30 mg, 8%) . M.p. 105-107 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 2.55 (s, 3H), 3.23 (s, 3H), δ 7.15 (m, 2H), 7.3 (m, 2H), 7.55 (m, 5H), 7.9 (d, 2H), 8.25 (s, 1H). MS (DCI-NH_3) m/z 485 $(M+H)^+$, 502 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{18}F_2N_2O_3S_2$: C, 59.49; H, 3.74; N, 5.78.

Example 260

2-Benzyl-4-(4-fluorophenyl)-5-[4-(trifluoromethylsulfonyl)phenyl]-3(2H)-pyridazinone:

260A. 2-Benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfinyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared starting with 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone and oxidizing the sulfide according to the procedure in example 69B.

260B. Bis(4-(5-(2-benzyl-4-(4-fluorophenyl)-3(2H)-pyridazinone)phenyl)disulfide:

A heterogeneous solution of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfinyl)phenyl]-3(2H)-pyridazinone (1.0 g, 2.39 mmol) in trifluoroacetic anhydride (10 mL, 70.8 mmol) was rapidly stirred at reflux for 2 hours with a bath temperature of 40-43 °C. The reaction solution was cooled to 23 °C, concentrated *in vacuo*, and azeotroped with toluene (2 x 5-7 mL). The resultant yellow/orange oil was cooled to 0 °C, and methanol/triethylamine (1:1, 6 mL) was slowly added, along the interior wall of the reaction vessel with rapid stirring. The bright red-orange solution was stirred for 10 minutes at 0 °C, the cooling bath removed, and the reaction mixture stirred an additional 1.5 hours warming to 23 °C. The mixture was cooled back to 0 °C, and a saturated NH_4Cl solution (200 mL) slowly added followed by enough aqueous 1 M HCl to adjust the solution to pH 1-2. The cooling bath was removed and the solution stirred overnight. The mixture was extracted with ethyl acetate. The ethyl acetate solution was washed with water and brine, and concentrated *in vacuo*. The resultant yellow/brown oil (0.89 g) was a mixture of predominantly the mono-sulfide and desired di-sulfide. Subsequent rapid stirring of a portion of the crude reaction mixture (360 mg) in benzene (100 mL) with I_2 (648 mg, 2.55 mmol) at 23 °C for 30 minutes completed the conversion of the mono-sulfide to the di-sulfide. (*Chem. Pharm. Bull.*, **1992**, *40*, 2842) The mixture was treated with a 0.1 M $Na_2S_2O_3$ solution to consume the excess I_2. This solution was extracted with ethyl acetate, and the ethyl acetate layers dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2/hexanes and concentrated *in vacuo* to provide the of product (yield: 347 mg, 90% for partial conversion). ^1H NMR (300 MHz, $CDCl_3$) δ 5.38 (s, 4H), 6.91 (dd, J = 8.8, 8.8 Hz, 4H), 7.02 (d, J = 8.7 Hz, 4H), 7.11-7.20 (m, 4H), 7.28-7.39 (m, 10H), 7.54 (dd, J = 6.9, 1.5 Hz, 4H), 7.83 (s, 2H).

260C. <u>2-Benzyl-4-(4-fluorophenyl)-5-[4-(trifluoromethylthio)phenyl]-3(2H)-pyridazinone</u>:

A rapidly stirred mixture of bis[4-{5-[2-benzyl-4-(4-fluorophenyl)-3(2H)-pyridazinone]}-phenyl]-disulfide (140 mg, 0.181 mmol), potassium trifluoroacetate (55 mg, 0.361 mmol), and sulfolane (1.5 mL) was immersed in a 180 °C pre-heated oil bath. The oil bath was heated to increase the temperature to 210 °C, and the reaction flask was promptly removed from the oil bath after 10 minutes from the point of first immersion. During the course of the reaction, the mixture changed from colorless and heterogeneous to deep, blood red and homogeneous. After cooling to 23 °C, the mixture was diluted with ethyl acetate and washed with aqueous 1 M HCl, water, and brine. The ethyl acetate solution was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was chromatographed (flash silica gel, ethyl acetate/hexanes 1:4) to provide the product (yield: 17 mg, 41%). (*Tetrahedron Lett.*., **1996**, *37*, 9057) ^1H NMR (300 MHz, $CDCl_3$) δ 5.41 (s, 2H), 6.94 (dd, J = 8.2, 8.2 Hz, 2H), 7.11-7.20 (m, 4H), 7.31-7.42 (m, 3H), 7.52-7.61 (m, 4H), 7.86 (s, 1H). MS (APCI+) m/z 457 $(M+H)^+$ and m/z 474 $(M+NH_4)^+$.

260D. <u>2-Benzyl-4-(4-fluorophenyl)-5-[4-(trifluoromethylsulfonyl)phenyl]-3(2H)-pyridazinone</u>:

A solution of 2-benzyl-4-(4-fluorophenyl)-5-[4-(trifluoromethylthio)phenyl]-3(2H)-pyridazinone (100 mg, 0.219 mmol), 3-chloroperoxybenzoic acid (380 mg, 1.3 mmol, 57-86%), and methylene chloride (5 mL) was brought to reflux at a bath temperature of 55 °C. After 1.75 hours, 3.5 hours, 5 hours, and 6 hours, the reaction was not complete and additional 3-chloroperoxybenzoic acid (380 mg, 1.3 mmol, 57-86%) was added each time. With the reaction completed after 7.75 hours, the mixture was cooled to 23 °C and concentrated *in vacuo*. The residue was diluted with ethyl acetate and carefully shaken with a $NaHSO_3$ solution, 3 times, for several minutes to consume the excess 3-chloroperoxybenzoic acid. The ethyl acetate solution was subsequently washed with a saturated Na_2CO_3 solution (3x), water, and brine and dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was chromatographed (flash silica gel, ethyl acetate/methylene chloride/hexanes 1:2:7) to provide of product (yield: 93 mg, 87%). (*J. Med. Chem.*, **1990**, *33*, 2569) M.p. 80-115 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 5.36 (s, 2H), 7.11 (dd, J = 9.0, 9.0 Hz, 2H), 7.18-7.26 (m, 2H), 7.29-7.46 (m, 5H), 7.66 (d, J = 8.7 Hz, 2H), 8.10 (d, J = 8.7 Hz, 2H), 8.18 (s, 1H). MS (APCI+) m/z 489 $(M+H)^+$ and m/z

506 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{16}F_4N_2O_3S$: C, 59.02; H, 3.30; N, 5.74. Found: C, 59.30; H, 3.48; N, 5.59.

Example 261

2-(2.2.2-Trifluoroethyl)-4-(2.2-dimethylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(2,2,2-Trifluoroethyl)-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (150 mg, 0.41 mmol), prepared in Example 193E, and neopentyl alcohol (43 mg, 0.49 mmol) were dissolved in DMF (2 mL) and NaH (25 mg, 0.62 mmol, 60% in mineral oil) was added with shaking and left overnight. The reaction mixture was carefully quenched with saturated NH_4Cl solution, diluted with ethyl acetate and extracted with 1 N HCl, twice, then water, 3 times, and then dried over $MgSO_4$. After filtration of the drying agent and concentration of the filtrate *in vacuo*, the residue was purified by chromatography on silica gel (Biotage 40S) eluted with 2:1 hexanes-ethyl acetate. The product fractions were combined and evaporated to provide the title compound (yield: 137 mg, 76%). M.p. 145-146 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 0.76 (s, 9H), 3.28 (s, 3H), 4.06 (s, 2H), 5.02 (q, J = 9 Hz, 2H), 7.88 (d, J = 8 Hz, 2H), 8.04 (d, J = 8 Hz, 2H), 8.13 (s, 1H). MS (DCI-NH_3) m/z 419 $(M+H)^+$, 436 $(M+NH_4)^+$. Anal. calc. for $C_{18}H_{21}F_3N_2O_4S$: C, 51.67; H, 5.06; N, 6.69. Found: C, 51.47; H, 5.12; N, 6.48.

Example 262

2-(2.2.2-Trifluoroethyl)-4-(4-methoxyphenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 4-methoxyphenol in place of neopentyl alcohol (yield: 130 mg, 54%). M.p. 194-195 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 2.24 (s, 3H), 3.26 (s, 3H), 5.00 (q, J = 9 Hz, 2H), 6.88 (d, J = 8 Hz, 2H), 7.09 (d, J = 8 Hz, 2H), 7.37 (d, J = 8 Hz, 2H), 8.03 (d, J = 8 Hz, 2H), 8.33 (s, 1H). MS (ESI-) m/z 439 $(M-H)^-$. Anal. calc. for $C_{19}H_{17}F_3N_2O_4S$: C, 54.79; H, 3.91; N, 6.39. Found: C, 55.04; H, 4.00; N, 6.11.

Example 263

2-(2.2.2-Trifluoroethyl)-4-(2-fluoro-5-trifluoromethylphenoxy)-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 2-fluoro-5-trifluoromethylphenol in place of neopentyl alcohol (yield:

155 mg, 89%). M.p. 133-135 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.28 (s, 3H), 5.03 (q, J = 9 Hz, 2H), 7.10-7.53 (m, 2H), 7.72 (dd, J = 1 Hz, 7 Hz 1H), 7.92 (d, J = 8 Hz, 2H), 8.07 (d, J = 8 Hz, 2H), 8.38 (s, 1H). MS (DCI-NH_3) m/z 528 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{13}F_7N_2O_4S$: C, 47.66; H, 3.09; N, 5.05. Found: C, 47.68; H, 2.95; N, 5.16.

Example 264

2-(2,2,2-Trifluoroethyl)-4-(4-cyanophenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 4-cyanophenol in place of neopentyl alcohol (yield: 109 mg, 71%). M.p. 179-181 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.26 (s, 3H), 5.02 (q, J = 9 Hz, 2H), 7.25 (d, J = 9 Hz, 2H), 7.81 (d, J = 9 Hz, 2H), 7.86 (d, J = 8 Hz, 2H), 8.03 (d, J = 8 Hz, 2H), 8.37 (s, 1H). MS (DCI-NH_3) m/z 467 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{14}F_3N_3O_4S$: C, 53.45; H, 3.14; N, 9.35. Found: C, 53.19; H, 3.01; N, 9.09.

Example 265

2-(2,2,2-Trifluoroethyl)-4-(3-pyridyloxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 3-hydroxypyridine in place of neopentyl alcohol (yield: 120 mg, 69%). M.p. 191-193 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.26 (s, 3H), 5.01 (q, J = 9 Hz, 2H), 7.36 (dd, J = 3 Hz, 8 Hz, 1H), 7.55 (ddd, J = 1 Hz, 3 Hz, 8 Hz, 1H), 7.88 (d, J = 8 Hz, 2H), 8.04 (d, J = 8 Hz, 2H), 8.31 (dd, J = 1 Hz, 5 Hz, 1H), 8.36 (s, 1H), 8.38 (d, J = 3 Hz, 1H). MS (DCI-NH_3) m/z 426 $(M+H)^+$, 443 $(M+NH_4)^+$. Anal. calc. for $C_{18}H_{14}F_3N_3O_4S$: C, 50.82; H, 3.32; N, 9.88. Found: C, 50.95; H, 3.57; N, 9.71.

Example 266

2-(2,2,2-Trifluoroethyl)-4-(4-n-propylphenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 4-(n-propyl)phenol in place of neopentyl alcohol (yield: 147 mg, 77%). M.p. 152-153 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.87 (t, J = 7 Hz, 3H), 1.54 (h, J = 7 Hz, 2H), 3.25 (s, 3H), 5.00 (q, J = 9 Hz, 2H), 6.88 (d, J = 9 Hz, 2H), 7.09 (d, J = 9 Hz, 2H), 7.87 (d, J = 8 Hz, 2H), 8.02 (d, J = 8 Hz, 2H), 8.32 (s, 1H). MS (DCI-NH_3)

m/z 484 (M+H)+. Anal. calc. for $C_{22}H_{21}F_3N_2O_4S$: C, 56.33; H, 4.54; N, 6.01. Found: C, 56.23; H, 4.75; N, 5.79.

Example 267

2-(2,2,2-Trifluoroethyl)-4-[4-(methylsulfonyl)phenoxy]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 4-(methylsulfonyl)phenol in place of neopentyl alcohol (yield: 115 mg, 56%). M.p. 212-213 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.21 (s, 3H), 3.27 (s, 3H), 5.03 (q, J = 9 Hz, 2H), 7.31 (d, J = 9 Hz, 2H), 7.83-7.89 (m, 4H), 8.04 (d, J = 8 Hz, 2H), 8.40 (s, 1H). MS (DCI-NH_3) m/z 520 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{17}F_3N_2O_6S_2$: C, 47.81; H, 3.41; N, 5.58. Found: C, 47.92; H, 3.18; N, 5.52.

Example 268

2-(2,2,2-Trifluoroethyl)-4-(4-phenylphenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 4-phenylphenol in place of neopentyl alcohol (yield: 105 mg, 51%). M.p. 163-165 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.26 (s, 3H), 5.02 (q, J = 9 Hz, 2H), 7.10 (d, J = 8 Hz, 2H), 7.33 (br t, J = 7 Hz, 1H), 7.44 (t, J = 7 Hz, 2H), 7.57-7.63 (m, 4H), 7.92 (d, J = 8 Hz, 2H), 8.04 (d, J = 8 Hz, 2H), 8.37 (s, 1H). MS (DCI-NH_3) m/z 518 $(M+NH_4)^+$. Anal. calc. for $C_{25}H_{19}F_3N_2O_4S$: C, 60.00; H, 3.83; N, 5.60. Found: C, 60.18; H, 3.66; N, 5.52.

Example 269

2-(2,2,2-Trifluoroethyl)-4-[2-(methylthio)ethoxy]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 2-(methylthio)ethanol in place of neopentyl alcohol (yield: 105 mg, 61%). M.p. 103-105 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.01 (s, 3H), 2.72 (t, J = 7 Hz, 2H), 3.29 (s, 3H), 4.59 (t, J = 7 Hz, 2H), 5.03 (q, J = 9 Hz, 2H), 7.91 (d, J = 8 Hz, 2H), 8.04 (d, J = 8 Hz, 2H), 8.15 (s, 1H). MS (DCI-NH_3) m/z 423 $(M+H)^+$, 440 $(M+NH_4)^+$. Anal. calc. for $C_{16}H_{17}F_3N_2O_4S_2$: C, 45.49; H, 4.06; N, 6.33. Found: C, 45.83; H, 4.11; N, 6.42.

Example 270

2-(2,2,2-Trifluoroethyl)-4-(phenylmethoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting benzyl alcohol in place of neopentyl alcohol (yield: 137 mg, 76%). M.p. 121-123 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.28 (s, 3H), 5.06 (q, J = 9 Hz, 2H), 5.48 (s, 2H), 7.20-7.25 (m, 2H), 7.27-7.81 (m, 3H), 7.76 (d, J = 8 Hz, 2H), 7.98 (d, J = 8 Hz, 2H), 8.12 (s, 1H). MS (DCI-NH_3) m/z 456 $(M+H)^+$. Anal. calc. for $C_{20}H_{17}F_3N_2O_4S$: C, 54,79; H, 3.91; N, 6.39. Found: C, 55.10; H, 3.91; N, 6.13.

Example 271

2-(2,2,2-Trifluoroethyl)-4-(2-furylmethoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 2-(hydroxymethyl)furan in place of neopentyl alcohol (yield: 101 mg, 58%). M.p. 113-115 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.28 (s, 3H), 5.07 (q, J = 9 Hz, 2H), 5.52 (s, 2H), 6.41 (dd, J = 2 Hz, 3 Hz, 1H), 6.45 (d, J = 4 Hz, 1H), 7.62 (d, J = 2 Hz, 1H), 7.69 (d, J = 8 Hz, 2H), 7.97 (d, J = 8 Hz, 2H), 8.13 (s, 1H). MS (DCI-NH_3) m/z 446 $(M+NH_4)^+$. Anal. calc. for $C_{18}H_{15}F_3N_2O_5S$: C, 50.66; H, 3.80; N, 6.21. Found: C, 51.02; H, 3.71; N, 6.23.

Example 272

2-(2,2,2-Trifluoroethyl)-4-[2-(3,4-dimethoxyphenyl)ethoxy)]-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 2-(3,4-dimethoxyphenyl)ethanol in place of neopentyl alcohol (yield: 118 mg, 56%). M.p. 133-134 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.82 (t, J = 7 Hz, 2H), 3.28 (s, 3H), 3.63 (s, 3H), 3.70 (s, 3H), 4.68 (t, J = 7 Hz, 2H), 5.01 (q, J = 9 Hz, 2H), 6.61 (dd, J = 2 Hz, 8 Hz, 1H), 6.74 (d, J = 2 Hz, 1H), 6.77 (d, J = 8 Hz, 1H), 7.74 (d, J = 8 Hz, 2H), 7.93 (d, J = 8 Hz, 2H), 8.11 (s, 1H). MS (DCI-NH_3) m/z 530 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{23}F_3N_2O_6S$: C, 53.90; H, 4.52; N, 5.47. Found: C, 53.87; H, 4.48; N, 5.45.

Example 273

2-(2,2,2-Trifluoroethyl)-4-[2-(4-morpholino)ethoxy)]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 4-(2-hydroxyethyl)morpholine in place of neopentyl alcohol (yield: 111 mg, 59%). M.p. 147-148 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.23 (m, 4H), 2.46 (t, J = 5 Hz, 2H), 3.28 (s, 3H), 3.40 (m, 4H), 4.60 (t, J = 5 Hz, 2H), 5.02 (q, J = 8 Hz, 2H), 7.96 (d, J = 8 Hz, 2H), 8.03 (d, J = 8 Hz, 2H), 8.17 (s, 1H). MS (DCI-NH_3) m/z 462 $(M+H)^+$. Anal. calc. for $C_{19}H_{22}F_3N_3O_5S$: C, 49.45; H, 4.81; N, 9.11. Found: C, 49.59; H, 4.80; N, 8.88.

Example 274

2-(2,2,2-Trifluoroethyl)-4-[2-(1-piperidinyl)ethoxy)]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 1-(2-hydroxyethyl)piperidine in place of neopentyl alcohol (yield: 103 mg, 55%). M.p. 117-118 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.30 (br s, 6H), 2.20 (br s, 4H), 2.41 (t, J = 4 Hz, 2H), 3.28 (s, 3H), 4.60 (t, J = 5 Hz, 2H), 5.02 (q, J = 9 Hz, 2H), 7.97 (d, J = 8 Hz, 2H), 8.03 (d, J = 8 Hz, 2H), 8.15 (s, 1H). MS (DCI-NH_3) m/z 460 $(M+H)^+$. Anal. calc. for $C_{20}H_{24}F_3N_3O_4S$: C, 52.28; H, 5.26; N, 9.15. Found: C, 52.22; H, 5.08; N, 8.94.

Example 275

2-(2,2,2-Trifluoroethyl)-4-[4-(carboxamido)phenoxy)]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 4-hydroxybenzamide in place of neopentyl alcohol (yield: 50 mg, 26%). M.p. > 250 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.26 (s, 3H), 5.02 (q, J = 8 Hz, 2H), 7.08 (d, J = 9 Hz, 2H), 7.30 (s, 1H), 7.82 (d, J = 9 Hz, 2H), 7.88 (d, J = 8 Hz, 2H), 7.92 (s, 1H), 8.03 (d, J = 8 Hz, 2H), 8.47 (s, 1H). MS (DCI-NH_3) m/z 468 $(M+H)^+$, 485 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{16}F_3N_3O_5S$: C, 51.39; H, 3.45; N, 8.99. Found: C, 51.31; H, 3.28; N, 8.77.

Example 276

2-(2,2,2-Trifluoroethyl)-4-(1-indanyloxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 1-indanol in place of neopentyl alcohol (yield: 84 mg, 44%). M.p. 113-114 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.07-2.14 (m, 1H), 2.22-2.35 (m, 1H), 2.73 (dd, J = 5 Hz, 7 Hz, 2H), 3.24 (s, 3H), 5.00-5.22 (m, 2H), 6.48 (dd, J = 2 Hz, 6 Hz, 1H), 7.12-7.24 (m, 2H), 7.21-7.28 (m, 2H), 7.44 (d, J = 8 Hz, 2H), 7.87 (d, J = 8 Hz, 2H), 8.09 (s, 1H). MS (DCI-NH_3) m/z 482 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{19}F_3N_2O_4S$: C, 57.19; H, 4.48; N, 5.80. Found: C, 57.36; H, 4.30; N, 5.78.

Example 277

2-(2,2,2-Trifluoroethyl)-4-[4-(acetamido)phenoxy)]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 4-acetamidophenol in place of neopentyl alcohol (yield: 45 mg, 23%). M.p. 215-216 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.02 (s, 3H), 3.26 (s, 3H), 5.02 (q, J = 8 Hz, 2H), 6.61-6.65 (m, 1H), 7.17-7.20 (m, 2H), 7.34 (br s, 1H), 7.88 (d, J = 9 Hz, 2H), 8.03 (d, J = 8 Hz, 2H), 8.36 (s, 1H), 9.97 (s, 1H). MS (DCI-NH_3) m/z 499 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{18}F_3N_3O_5S$: C, 52.39; H, 3.77; N, 8.73. Found: C, 52.57; H, 4.02; N, 8.37.

Example 278

2-(2,2,2-Trifluoroethyl)-4-(2-methylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 2-methylpropanol in place of neopentyl alcohol (yield: 111 mg, 50%). M.p. 108-110 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.77 (d, J = 6.4 Hz, 6H), 1.52 (sept, J = 6.4 Hz, 1H), 3.28 (s, 3H), 4.17 (d, J = 6 Hz, 2H), 5.02 (q, J = 9 Hz, 2H), 7.88 (d, J = 9 Hz, 2H), 8.04 (d, J = 9 Hz, 2H), 8.14 (s, 1H). MS (DCI-NH_3) m/z 405 $(M+H)^+$, 422 $(M+NH_4)^+$. Anal. calc. for $C_{17}H_{19}F_3N_2O_4S$: C, 50.49; H, 4.74; N, 6.93. Found: C, 50.69; H, 4.89; N, 6.75.

Example 279

2-(2,2,2-Trifluoroethyl)-4-(1-methylcyclopropylmethoxy)-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 1-methylcyclopropanemethanol in place of neopentyl alcohol (yield: 360 mg, 75.5%). M.p. 98-99 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.35 (dt, J = 40 Hz, 5 Hz, 4H), 0.91 (s, 3H), 3.11 (s, 3H), 4.32 (s, 2H), 4.82 (q, J = 8.5 Hz, 2H), 7.80 (d, J = 8.5 Hz, 2H), 7.84 (s, 1H), 8.06 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 417 $(M+H)^+$, m/z 434 $(M+NH_4)^+$. Anal. calc. for $C_{18}H_{19}F_3N_2O_4S$: C, 51.92; H, 4.60; N, 6.73. Found: C, 51.87; H, 4.72; N, 6.69.

Example 280

2-(2,2,2-Trifluoroethyl)-4-(3,3-dimethylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 3,3-dimethyl-1-butanol in place of neopentyl alcohol (yield: 270 mg, 67.4%). M.p. 83-85 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (s, 9H), 1.56 (t, J = 8 Hz, 2H), 4.60 (t, J = 8 Hz, 2H), 4.83 (q, J = 8.5 Hz, 2H), 7.73 (d, J = 8.5 Hz, 2H), 7.81 (s, 1H), 8.05 (d, J = 8.5 Hz, 2H). MS (DCI-NH_3) m/z 433 $(M+H)^+$, m/z 450 $(M+NH_4)^+$. Anal. calc. for $C_{19}H_{23}F_3N_2O_4S$: C, 52.77; H, 5.36; N, 6.48. Found: C, 52.95; H, 5.29; N, 6.35.

Example 281

2-(3,4-Difluorophenyl)-4-(4-chlorophenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A mixture of 2-benzyl-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (187 mg, 0.5 mmol), prepared in Example 78, p-chlorophenol (129 mg, 0.5 mmol) and NaH (60% oil suspension) (40 mg, 1 mmol) in THF (25 mL) was refluxed at 50 °C for 3 hours and then concentrated *in vacuo*. The residue was partitioned between water and ethyl acetate. The acetate layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (silica gel, 1:1 hexanes-ethyl acetate) to provide 2-benzyl-4-(4-chlorophenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 200 mg, 82%).

The above derivative was dissolved in toluene (25 mL) and was treated with $AlBr_3$ (400 mg, 1.5 mmol) for 20 minutes at 80 °C. The mixture was cooled to room temperature and poured into ice-10% citric acid-ethyl acetate. The organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo* to provide crude desbenzyl derivative. This compound was immediately dissolved in pyridine (50

mL) and was treated with 3,4-difluorobromobenzene (0.17 mL, 1.5 mmol), Cu (20 mg) and K_2CO_3 (100 mg, 1.5 mmol) at reflux for 16 hours. After the mixture was concentrated *in vacuo*, the residue was dissolved in ethyl acetate and was washed with water, 10% citric acid and brine. Purification by column chromatography (silica gel, 1:1 hexanes-ethyl acetate) provided the title compound (yield: 73 mg, 30%). M.p. 192-194 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 3.22 (s, 3H), 7.13 (m, 2H), 7.35 (m, 2H), 7.50 (m, 1H), 7.60 (m, 1H), 7.75 (m, 1H), 7.87 (d, J = 9 Hz, 2H), 8.05 (d, J = 9 Hz, 2H), 8.41 (s, 1H). MS (APCI+) m/z 488 $(M+H)^+$ and (APCI-) m/z 523 $(M+Cl)^-$.

Example 282

2-(3,4-Difluorophenyl)-4-(4-bromophenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

The title compound was prepared according to the method of Example 281, substituting p-bromophenol in place of p-chlorophenol (yield: 54 mg, 20%). M.p. 196-199 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 3.25 (s, 3H), 7.09 (d, J = 9 Hz, 2H), 7.47 (d, J = 9 Hz, 2H), 7.52 (m, 1H), 7.62 (m, 1H), 7.78 (m, 1H), 7.89 (d, J = 9 Hz, 2H), 8.05 (d, J = 9 Hz, 2H), 8.41 (s, 1H). MS (APCI+) m/z 533 $(M+H)^+$ and (APCI-) m/z 569 $(M+Cl)^-$.

Example 283

2-(2,2,2-Trifluoroethyl)-4-(cyclopentylthio)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

To a solution of NaH (26 mg, 1.1 mmol) in acetonitrile (3.0 mL), under nitrogen, was added cyclopentyl mercaptan (120 μL, 1.1 mmol) dropwise via syringe. The resulting solution was flushed with nitrogen for a period of 20 minutes; after which 2-(trifluoroethyl)-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, prepared in Example 193E, (200 mg, 0.52 mmol) was added in one portion. The solution was stirred for an additional 20 minutes at which time, all the 4-bromo pyridazinone was consumed. The solution was analyzed by TLC (1:1, ethyl acetate-Hex). Water (5 mL) was carefully added and the reaction partitioned between ethyl acetate (125 mL) and saturated saline (50 mL). The organic layer is washed with saturated saline (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Silica gel chromatography (20% ethyl acetate-80% hexanes) provided a pale yellow solid (yield: 202 mg, 83.1%). M.p. 149-151 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.40-1.34 (m, 2H), 1.62-1.54 (m, 4H), 1.93-1.88 (m, 2H), 3.13 (s, 3H), 4.40-4.35 (m, 1H), 4.85 (q, J = 8.2 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 7.66 (s, 1H),

8.06 (d, J = 8.4 Hz, 2H). MS (DCI-NH_3) m/z 432 $(M+H)^+$, $(M+NH_4)^+$. Anal. calc. for $C_{18}H_{19}F_3N_2O_3S_2$: C, 49.99; H, 4.43; N, 6.48. Found: C, 50.15; H, 4.39; N, 6.45.

Example 284

2-(2,2,2-Trifluoroethyl)-4-(1H-1,2,4-triazole-3-ylthio)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

The title compound was prepared according to the method of Example 283, substituting 1H-1,2,4-triazole-3-thiol in place of cyclopentyl mercaptan (yield: 164 mg, 93%). M.p. 197-200 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.14 (s, 3H), 4.84 (q, J = 8.1 Hz, 2H), 7.41 (s, 1H), 7.68 (d, J = 6.8 Hz, 2H), 7.83 (s, 1H), 8.00 (d, J = 7.1 Hz, 2H), 8.05 (s, 1H). MS (DCI-NH_3) m/z 431 $(M+H)^+$, $(M+NH_4)^+$. Anal. calc. for $C_{15}H_{12}F_3N_2O_3S_2$: C, 41.76; H, 2.80 ; N, 16.23. Found: C, 41.68; H, 2.85; N, 15.99.

Example 285

2-(2,2,2-Trifluoroethyl)-4-phenylmethylthio-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

The title compound was prepared according to the method of Example 283, substituting benzyl mercaptan in place of cyclopentyl mercaptan (yield: 141 mg, 76%). M.p. 108-111 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.01 (s, 3H), 4.38 (s, 2H), 4.87 (q, J = Hz, 2H), 7.10-7.06 (m, 2H), 7.22-7.20 (m, 5H), 7.59 (s, 1H), 7.95 (d, J = 8.5 Hz, 2H). MS (DCI-NH_3) m/z 454 $(M+H)^+$, $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{17}F_3N_2O_3S_2$, 0.75 EtOAc: C, 53.06; H, 4.45 ; N, 5.38. Found: C, 53.55; H, 4.16; N, 5.84.

Example 286

2-(2,2,2-Trifluoroethyl)-4-(4-fluorophenylthio)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 283, substituting 4-fluorophenylmethyl mercaptan in place of cyclopentyl mercaptan (yield: 184 mg, 73.5%). M.p. 182-185 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.08 (s, 3H), 4.82 (q, J = 8.5 Hz, 2H), 6.87-6.81 (m, 2H), 7.19-7.11 (m, 2H), 7.48 (d, J = 9.0 Hz, 2H), 7.68 (s, 1H), 7.93 (d, J = 8.5 Hz, 2H). MS (DCI-NH_3) m/z 458 $(M+H)^+$, $(M+NH_4)^+$. Anal. calc. for $C_{19}H_{14}F_4N_2O_3S_2$: C, 49.78; H, 3.08 ; N, 6.11. Found: C, 49.89 ; H, 3.18 ; N, 5.86

Example 287

2-(2,2,2-Trifluoroethyl)-4-(cyclohexylthio)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 283, substituting cyclohexyl mercaptan in place of cyclopentyl mercaptan (yield: 189 mg, 78%). M.p. 165-167 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28-1.17 (m, 5H), 1.64-1.56 (m, 3H), 1.82-1.79 (m, 2H), 3.13 (s, 3H), 4.08-4.05 (m, 1H), 4.86 (q, J = 8.5 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.67 (s, 1H), 8.06 (d, J = 8.5 Hz, 2H). MS (DCI-NH_3) m/z 446 $(M+H)^+$, $(M+NH_4)^+$. Anal. calc. for $C_{19}H_{21}F_3N_2O_3S_2$: C, 51.11; H, 4.74 ; N, 6.27. Found: C, 51.39 ; H, 4.72 ; N, 5.91.

Example 288

2-(2,2,2-Trifluoroethyl)-4-(3-chloro-4-fluorophenylthio)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 283, substituting 3-chloro-4-fluorothiophenol in place of cyclopentyl mercaptan (yield: 190 mg, 65%). M.p. 142-145 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.18 (s, 3H), 4.85 (q, J = 8.4 Hz, 2H), 6.96 (ov. t, J = 8.5 Hz, 1H), 7.14-7.10 (m, 1H), 7.18 (dd, J = 2.1, 6.5 Hz, 1H,), 7.53 (d, J = 8.4 Hz, 2H), 7.77 (s, 1H), 7.96 (d, J = 8.0 Hz, 2H). MS (CI) m/z 493 $(M+1)^+$, $(M+NH_4)^+$. Anal. calc. for $C_{19}H_{13}ClF_4N_2O_3S_2$.0.25 $C_6H_6 \cdot H_2O$: C, 47.36 ; H, 2.92; N, 5.41. Found: C, 47.88 ; H, 2.95; N, 5.24.

Example 289

2-(2,2,2-Trifluoroethyl)-4-(2,2,2-trifluoroethylthio)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

The title compound was prepared according to the method of Example 283, substituting 2,2,2-trifluoroethyl mercaptan in place of cyclopentyl mercaptan (yield: 175 mg, 66%). M.p. 155-158 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.14 (s, 3H), 3.98 (q, J = 9.8 Hz, 2H), 4.86 (q, J = 8.1 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.75 (s, 1H), 8.10 (d, J = 8.4 Hz, 2H). MS (DCI-NH_3) m/z 446 $(M+H)^+$, $(M+NH_4)^+$. Anal. calc. for $C_{15}H_{12}F_6N_2O_3S_2$: C, 40.36 ; H, 2.71; N, 6.28. Found: C, 40.50; H, 2.72; N, 6.01.

Example 290

2-(2,2,2-Trifluoroethyl)-4-(*tert*-butylthio)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

The title compound was prepared according to the method of Example 283, substituting *tert*-butyl mercaptan in place of cyclopentyl mercaptan (yield: 212 mg, 85%). M.p. 186-189 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 9H), 3.13 (s, 3H), 4.87 (q, J = 8.1 Hz, 2H), 7.62 (d, J = 8.5 Hz, 2H), 7.67 (s, 1H), 8.05 (d, J = 8.1 Hz, 2H). MS (ESI) m/z 420 $(M+H)^+$, $(M+Na)^+$. Anal. calc. for $C_{17}H_{19}F_3N_2O_3S_2$: C, 48.56 ; H, 4.55; N, 6.66. Found: C, 50.15; H, 4.39; N, 6.45.

Example 291

2-(2,2,2-Trifluoroethyl)-4-(4-acetamidophenylthio)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

The title compound was prepared according to the method of Example 283, substituting 4-acetamidothiophenol in place of cyclopentyl mercaptan (yield: 100 mg, 37%). M.p. 191-193 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 2.16 (s, 3H), 3.08 (s, 3H), 4.83 (q, J = 8.2 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 8.8 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 7.58 (s, 1H), 7.78 (d, J = 8.1 Hz, 2H). MS (CI) m/z 497 $(M+H)^+$, $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{18}F_3N_3O_4S_2 \cdot 0.25H_2O$, 0.25 C_6H_6: C, 52.83; H, 4.06; N, 7.70. Found: C, 52.97; H, 3.85; N, 7.65.

Example 292

2-(2,2,2-Trifluoroethyl)-4-(2-propylthio)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

The title compound was prepared according to the method of Example 283, substituting isopropyl mercaptan in place of cyclopentyl mercaptan (yield: 180 mg, 81%). M.p. 165-167 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (d, J = 6.8 Hz, 6H), 3.13 (s, 3H), 4.33 (p, J = 6.8 Hz, 1H), 4.86 (q, J = 8.5 Hz, 2H), 6.59 (d, J = 8.5 Hz, 2H), 7.68 (s, 1H), 8.07 (d, J = 8.1 Hz, 2H). MS (DCI-NH_3) m/z 406 $(M+H)^+$, $(M+NH_4)^+$. Anal. calc. for $C_{16}H_{17}F_3N_2O_3S_2$, $0.75H_2O$: C, 45.76 ; H, 4.4; N, 6.67. Found: C, 45.91; H, 3.98; N, 6.46.

Example 293

2-(2,2,2-Trifluoroethyl)-4-(2-methylprop-1-ylthio)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

The title compound was prepared according to the method of Example 283, substituting 2-methyl-1-propyl mercaptan in place of cyclopentyl mercaptan (yield: 100 mg, 83%). M.p. 135-138 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, J = 6.4 Hz, 6H), 1.67-1.60 (m, 1H), 3.00 (d, J = 6.7 Hz, 2H), 3.14 (s, 3H), 4.84 (q, J = 8.5 Hz,

2H), 7.61 (d, J = 8.4 Hz, 2H), 7.67 (s, 1H), 8.08 (d, J = 8.5 Hz, 2H). MS (DCI-NH_3) m/z 420 $(M+H)^+$, $(M+NH_4)^+$. Anal. calc. for $C_{17}H_{19}F_3N_2O_3S_2$: C, 48.56 ; H, 4.55; N, 6.66. Found: C, 47.86; H, 4.57; N, 6.51.

Example 294

2-(2,2,2-Trifluoroethyl)-4-amino-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(2,2,2-Trifluoroethyl)-4-chloro-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone, prepared according to Example 193E, (500 mg, 1.36 mmol) was dissolved in DMF (10 mL) and treated with NaN_3 (100 mg, 1.5 mmol). After 2 hours at room temperature, the reaction was diluted with ethyl acetate and washed with water, 4 times, and dried over $MgSO_4$. After filtration of the drying agent and concentration of the filtrate *in vacuo*, the residue was purified by chromatography on silica gel (Biotage 40S) eluted with 2:1 hexanes-ethyl acetate. The product fractions were combined and evaporated to provide the azido intermediate, 2-(2,2,2-Trifluoroethyl)-4-azido-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (yield: 481 mg, 95%).

The 4-azido-compound above (39 mg, 0.105 mmol) was dissolved in THF (3 mL) and MeOH (2 mL) and treated with excess $NaBH_4$. After 15 minutes, the reaction was quenched with saturated NH_4Cl solution and the product was extracted into ethyl acetate. The organic layer was washed with water, 3 times, and dried over $MgSO_4$. Filtration of the drying agent and evaporation of the solvent provided the title compound (yield: 26 mg, 71%). M.p. > 260 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 3.26 (s, 3H), 4.93 (q, J = 9 Hz, 2H), 6.71 (s, 2H), 7.72 (s, 1H), 7.76 (d, J = 8 Hz, 2H), 8.02 (d, J = 8 Hz, 2H). MS (ESI-) m/z 346 $(M-H)^-$. Anal. calc. for $C_{13}H_{12}F_3N_3O_3S$: C, 44.96; H, 3.48; N, 12.10. Found: C, 44.59; H, 3.52; N, 11.93.

Example 295

2-(2,2,2-Trifluoroethyl)-4-(3-methoxypropylamino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A solution of 2-(2,2,2-trifluoroethyl)-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (200 mg, 0.546 mmol), prepared according to the method of Example 193E, and 3-methoxypropylamine (145 mg, 1.64 mmol) in pyridine (4 mL) was heated at 100 °C for 16 hours. The reaction mixture was cooled to room temperature, mixed with silica gel (2 g), and the solvent removed under reduced pressure. The adsorbed silica gel was layered over an Extract-Clean Cartridge®

(Alltech, packing: 10 g silica gel) and the cartridge eluted with a hexanes/acetone step gradient consisting of 60 mL of each of the following mixtures: hexanes, 8:1 hexanes/acetone, 4:1, 2:1, and 1:1. Fractions containing desired product were combined, concentrated, and further purified using HPLC (Technikrom Kromasil 60-5 sil silica column, 20 mm x 25 cm). The column was eluted with a linear gradient consisting of 30% ethyl acetate/hexanes to 100% ethyl acetate at 10 mL/min over 50 minutes. Fractions containing product were combined and concentrated under reduced pressure to provide the product as off-white crystals (yield: 215 mg, 95%). M.p. 110-113 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 18.0 Hz, 2H), 7.55 (d, 2H, J = 18.0 Hz), 7.48 (s, 1H), 6.57 (br t, 1H, J = 9.0 Hz), 4.81 (q, J = 17.4 Hz, 2H), 3.33 (t, J = 12.0 Hz, 2H), 3.28 (s, 3H), 3.12 (s, 3H), 2.76 (dt, J = 12.0, 12.0 Hz, 2H), 1.65 (tt, J = 12.0, 12.0, Hz, 2H). MS (DCI-NH_3) m/z 420 $(M+H)^+$, m/z 437 $[M+NH_4]^+$. Anal. calc. for $C_{17}H_{20}F_3N_3O_4S$: C, 48.68; H, 4.81; N, 10.02. Found: C, 48.74; H, 4.69; N, 9.84.

Example 296

2-(2,2,2-Trifluoroethyl)-4-(cyclopentylamino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 295, substituting cyclopentylamine in place of 3-methoxypropylamine to provide brown crystals (yield: 195 mg, 86%). M.p. 134-139 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 18.0 Hz, 2H), 7.56 (d, J = 18.0 Hz, 2H), 7.45 (s, 1H), 6.12 (br d, J = 16.8 Hz, 1H), 4.79 (q, J = 17.4 Hz, 2H), 3.33 (br m, 1H), 3.12 (s, 3H), 1.64-1.23 (br m, 8H). MS (DCI-NH_3) m/z 416 $(M+H)^+$, m/z 433 $(M+NH_4)^+$. Anal. calc. for $C_{18}H_{20}F_3N_3O_3S$: C, 52.04; H, 4.85; N, 10.11. Found: C, 52.40; H, 4.93; N, 10.03.

Example 297

2-(2,2,2-Trifluoroethyl)-4-(cyclobutylamino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 295, substituting cyclobutylamine in place of 3-methoxypropylamine to provide an off-white solid (yield: 206 mg, 94%). M.p. 169-172 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 17.4 Hz, 2H), 7.54 (d, J = 17.4 Hz, 2H), 7.45 (s, 1H), 6.28 (br d, J = 16.2 Hz, 1H), 4.81 (q, J = 17.4 Hz, 2H), 3.42 (m, 1H), 3.13 (s, 3H), 1.79 (m, 4H), 1.64 (m, 1H), 1.39 (m, 1H). MS (DCI-NH_3) m/z 402 $(M+H)^+$, m/z 419 $(M+NH_4)^+$. Anal calc.

for $C_{17}H_{18}F_3N_3O_3S \cdot 0.25\ CH_3COCH_3$: C, 51.25; H, 4.72; N, 10.10; found: C, 51.38; H, 4.68; N, 10.25.

Example 298

2-(2,2,2-Trifluoroethyl)-4-(3,4-dimethoxyphenethylamino)-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 295, substituting 3,4-dimethoxyphenethylamine in place of 3-methoxypropylamine to provide an off-white solid (yield: 206 mg, 94%). M.p. 163-165 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 18.0 Hz, 2H), 7.52 (d, J = 18.0 Hz, 2H), 7.45 (s, 1H), 6.75 (d, J = 16.2 Hz, 1H), 6.50 (m, 2H), 6.16 (br d, J = 11.4 Hz, 1H), 4.79 (q, J = 17.4 Hz, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.11 (s, 3H), 2.91 (dt, J = 12.6, 12.6 Hz, 2H), 2.60 (t, J = 13.8 Hz, 2H). MS (DCI-NH_3) m/z 529 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{24}F_3N_3O_5S$: C, 54.01; H, 4.73; N, 8.21. Found: C, 54.30; H, 4.69; N, 8.16.

Example 299

2-(2,2,2-Trifluoroethyl)-4-(cyclohexylamino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 295, substituting cyclohexylamine in place of 3-methoxypropylamine to provide an off-white solid (yield: 103 mg, 42%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 18.0 Hz, 2H), 7.58 (d, J = 18.0 Hz, 2H), 7.44 (s, 1H), 6.06 (br d, J = 18.6 Hz, 1H), 4.81 (q, J = 18.0 Hz, 2H), 3.11 (s, 3H), 2.70 (m, 1H), 1.66-1.48 (m, 4H), 1.42 (m, 1H), 1.07 (m, 3H), 0.76 (m, 2H). MS (DCI-NH_3) m/z 430 $(M+H)^+$, m/z 447 $(M+NH_4)^+$. Anal. calc. for $C_{19}H_{22}F_3N_3O_3S$: C, 53.14; H, 5.16; N, 9.78. Found: C, 52.86; H, 5.06; N, 9.52.

Example 300

2-(2,2,2-Trifluoroethyl)-4-[2-(1-piperidinyl)ethylamino]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 295, substituting cyclopentylamine in place of 3-methoxypropylamine to provide an off-white solid (yield: 210 mg, 84%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 18.0 Hz, 2H), 7.56 (d, J = 18.0 Hz, 2H), 7.49 (s, 1H), 6.91 (br, 1H), 4.82 (q, J = 18.0 Hz, 2H), 3.13 (s, 3H), 2.64 (br, 2H), 2.32 (br, 4H), 1.58 (br, 6H), 1.42 (br, 2H). MS (DCI-NH_3) m/z 459 $(M+H)^+$. Anal. calc. for $C_{19}H_{22}F_3N_3O_3S$: C, 52.39; H, 5.50; N, 12.22. Found: C, 52.64; H, 5.59; N, 12.00.

Example 301

2-(2.2.2-Trifluoroethyl)-4-(2-tetrahydrofurfurylamino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 295, substituting tetrahydrofurfurylamine in place of 3-methoxypropylamine to provide an off-white solid (yield: 150 mg, 64%). M.p. 128-129 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 18.0 Hz, 2H), 7.56 (d, J = 18.0 Hz, 2H), 7.47 (s, 1H), 6.48 (br t, J = 9.0 Hz, 1H), 4.81 (q, J = 18.0 Hz, 2H), 3.84 (m, 2H), 3.72 (m, 1H), 3.12 (s, 3H), 2.83 (m, 1H), 2.64 (m, 1H), 1.84 (m, 3H), 1.34 (m, 1H). MS (DCI-NH_3) m/z 432 $(M+H)^+$, m/z 449 $(M+NH_4)^+$. Anal. calc. for $C_{18}H_{20}F_3N_3O_3S$: C, 50.11; H, 4.67; N, 9.74. Found: C, 50.25; H, 4.68; N, 9.68.

Example 302

2-(2.2.2-Trifluoroethyl)-4-(cyclopropylamino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 295, substituting cyclopropylmethylamine in place of 3-methoxypropylamine to provide an off-white solid (yield: 130 mg, 59%). M.p. 145-146 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 18.0 Hz, 2H), 7.53 (d, J = 18.0 Hz, 2H), 7.48 (s, 1H), 6.20 (br, 1H), 4.82 (q, J = 18.0 Hz, 2H), 3.12 (s, 3H), 2.45 (br d, J = 13.2 Hz, 2H), 0.88 (m, 1H), 0.51 (m, 2H), 0.10 (m, 2H). MS (DCI-NH_3) m/z 402 $(M+H)^+$, m/z 419 $(M+NH_4)^+$. Anal. calc. for $C_{17}H_{18}F_3N_3O_3S$: C, 50.87; H, 4.52; N, 10.47. Found: C, 51.00; H, 4.52; N, 10.44.

Example 303

2-(2.2.2-Trifluoroethyl)-4-(2.3-dihydro-1H-inden-1-ylamino)-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 295, substituting 1-indanylamine in place of 3-methoxypropylamine to provide an off-white solid (yield: 82 mg, 32%). M.p. 155-158 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 18.0 Hz, 2H), 7.68 (d, J = 18.0 Hz, 2H), 7.49 (s, 1H), 7.27-7.14 (m, 4H), 6.30 (br d, J = 18.0 Hz, 1H), 4.81 (q, J = 18.0 Hz, 2H), 4.57 (m, 1H), 3.09 (s, 3H), 2.89 (m, 1H), 2.60 (m, 1H), 1.85 (m, 1H), 1.68 (m, 1H). MS (ESI (-) m/z 462 $(M-H)^-$. Anal. calc. for $C_{22}H_{20}F_3N_3O_3S$: C, 57.01; H, 4.35; N, 9.07. Found: C, 57.30; H, 4.45; N, 8.86.

Example 304

2-(2,2,2-Trifluoroethyl)-4-(1-piperidinyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 295, substituting piperidine in place of 3-methoxypropylamine to provide an off-white solid (yield: 180 mg, 79%). M.p. 160-161 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 18.0 Hz, 2H), 7.58 (s, 1H), 7.46 (d, J = 18.0 Hz, 2H), 4.80 (q, J = 18.0 Hz, 2H), 3.13 (s, 3H), 2.96 (m, 4H), 1.65-1.52 (m, 6H). MS (DCI-NH_3) m/z 416 $(M+H)^+$. Anal. calc. for $C_{18}H_{20}F_3N_3O_3S{\cdot}H_2O$: C, 52.04; H, 4.85; N, 10.11. Found: C, 52.21; H, 5.02; N, 9.75.

Example 305

2-(2,2,2-Trifluoroethyl)-4-(3-hydroxypropylamino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 295, substituting 3-hydroxypropylamine in place of 3-methoxypropylamine to provide a white solid (yield: 109.6 mg, 50%). M.p. 152-154 °C. ^1H NMR (300 MHz, CDCl3) δ 8.02 (d, J = 18.0 Hz, 2H), 7.56 (d, J = 18.0 Hz, 2H), 7.48 (s, 1H), 6.48 (br, 1H), 4.79 (q, J = 17.4 Hz, 2H), 3.63 (t, J = 12.0 Hz, 2H), 3.12 (s, 3H), 2.81 (dt, J = 12.0, 12.0 Hz, 2H), 1.65 (tt, J = 12.0, 12.0 Hz, 2H). MS (DCI-NH_3) m/z 406 $(M+H)^+$, m/z 423 $(M+NH_4)^+$. Anal. calc. for $C_{16}H_{18}F_3N_3O_4S$: C, 47.41; H, 4.48; N, 10.37. Found: C, 47.53; H, 4.33; N, 10.27.

Example 306

2-(2,2,2-Trifluoroethyl)-4-[3-(1H-imidazol-1-yl)propylamino]-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 295, substituting (3-aminopropyl)imidazole in place of 3-methoxypropylamine. The reaction mixture was concentrated to dryness and the residue purified using RP-HPLC (Rainin Dynamax C-18 column, 60 Å pore size, 21.4 mm i.d.). The column was eluted with a linear gradient consisting of 20% acetonitrile (containing 0.1% TFA)/80% water (containing 0.1% TFA) to 100% acetonitrile (containing 0.1% TFA) at 15 mL/min over 70 minutes. The peak corresponding to the title product was collected and lyophilized to provide a tan hygroscopic foam (yield: 70.2 mg, 28%). ^1H NMR (300 MHz, DMSO) δ 8.95 (br s, 1H), 7.97 (d, J = 16.8 Hz, 2H), 7.66 (d, J =

16.2 Hz, 2H), 7.61 (s, 1H), 7.58 (d, J = 15.0 Hz, 2H), 6.99 (br t, 1H, J = 13.2 Hz), 4.97 (dt, J = 18.0, 18.0 Hz, 2H), 3.97 (t, J = 13.2 Hz, 2H), 3.28 (s, 3H), 2.69 (m, 2H), 1.81 (tt, J = 13.2, 13.2 Hz, 2H). MS (DCI-NH_3) m/z 456 $(M+H)^+$. Anal. calc. for $C_{19}H_{20}F_3N_5O_3S \cdot 1.4\ CF_3COOH$: C, 42.57; H, 3.51; N, 11.39. Found: C, 42.78; H, 3.58; N, 11.24.

Example 307

2-(2,2,2-Trifluoroethyl)-4-(2R-hydroxylpropylamino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 295, substituting (R)-(-)-2-propanolamine in place of 3-methoxypropylamine to provide an off-white solid (yield: 109.6 mg, 50%). M.p . = 140-142 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 18.0 Hz, 2H), 7.56 (d, J = 18.0 Hz, 2H), 7.49 (s, 1H), 6.42 (br, 1H), 4.79 (m, 2H), 3.80 (m, 1H), 3.12 (s, 3H), 2.68 (m, 2H), 1.02 (d, J = 12.0 Hz, 3H). MS (DCI-NH_3) m/z 406 $(M+H)^+$, m/z 423 $(M+NH_4)^+$. Anal. calc. for $C_{16}H_{18}F_3N_3O_4S$: C, 47.41; H, 4.48; N, 10.37. Found: C, 47.56; H, 4.41; N, 10.25.

Example 308

2-(2,2,2-Trifluoroethyl)-4-(2-cyanoethylamino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 295, substituting 1-cyanoethylamine in place of 3-methoxypropylamine to provide an off-white solid (yield: 27 mg, 12%). M.p. 172-174 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, J = 18.0 Hz, 2H), 7.63 (d, J = 18.0 Hz, 2H), 7.51 (s, 1H), 6.08 (br t, 1H), 4.87 (q, J = 18.0 Hz, 2H), 3.17 (dt, J = 13.2, 13.2 Hz, 2H), 3.13 (s, 3H), 2.39 (t, J = 13.2 Hz, 2H). MS (DCI-NH_3) m/z 418 $(M+NH_4)^+$. Anal. calc. for $C_{16}H_{15}F_3N_4O_3S$: C, 48.00; H, 3.78; N, 13.99. Found: C, 48.28; H, 3.77; N, 13.80.

Example 309

2-(2,2,2-Trifluoroethyl)-4-(4-cyanoanilino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A suspension of 2-(2,2,2-trifluoroethyl)-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (300 mg, 0.820 mmol), prepared according to the method of Example 193E, 4-aminobenzonitrile (290 mg, 2.46 mmol), and silver oxide (760 mg, 3.28 mmol) in pyridine (1.5 mL) was stirred at 80 °C for 24 hours. The reaction was cooled to room temperature, adsorbed onto silica gel (2 g) and solvent

removed under reduced pressure. The adsorbed silica gel was layered over an Extract-Clean Cartridge® (Alltech, packing: 10 g silica gel) and the cartridge eluted with a hexanes/acetone step gradient consisting of 60 mL of each of the following mixtures: hexanes, 8:1 hexanes/acetone, 4:1, 2:1, and 1:1. Fractions containing desired product were combined, concentrated, and further purified using HPLC (Technikrom Kromasil 60-5sil column, 20 mm x 25 cm). The column was eluted with a linear gradient consisting of 30% ethyl acetate/hexanes to 100% ethyl acetate at 10 mL/min over 50 minutes. Fractions containing product were combined and concentrated under reduced pressure to provide the product as a tan solid (yield: 149.9 mg, 41%). M.p.>230 °C. ^{1}H NMR (300 MHz, DMSO) δ 9.49 (s, 1H), 8.00 (s, 1H), 7.69 (d, J = 17.4 Hz, 2H), 7.43 (d, J = 16.8 Hz, 2H), 7.32 (d, J = 18.0 Hz, 2H), 6.78 (d, J = 18.0 Hz, 2H), 5.06 (q, J = 18.0 Hz, 2H), 3.13 (s, 3H), 2.68 (m, 2H), 1.02 (d, J = 12.0 Hz, 3H). MS (DCI-NH_3) m/z 466 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{15}F_3N_4O_3S$: C, 53.57; H, 3.37; N, 12.49. Found: C, 53.47; H, 3.49; N, 12.35.

Example 310

2-(2,2,2-Trifluoroethyl)-4-[3-methoxy-5-(trifluoromethyl)anilino]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 309 , substituting 3-methoxy-5-(trifluoromethyl)aniline in place of 4-aminobenzonitrile to provide a brown solid (yield: 226.5 mg, 80%). M.p. 206-208 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.77 (s, 1H), 7.71 (d, J = 18.0 Hz, 2H), 7.28 (d, J = 17.4 Hz, 2H), 6.61 (br s, 1H), 6.46 (br s, 1H), 6.31 (br s, 1H), 4.90 (q, J = 17.4 Hz, 2H), 3.72 (s, 3H), 2.94 (s, 3H). MS (DCI-NH_3) m/z 539 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{17}F_6N_3O_4S$: C, 48.37; H, 3.29; N, 8.06. Found: C, 48.60; H, 3.33; N, 7.94.

Example 311

2-(2,2,2-Trifluoroethyl)-4-anilino-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 309 , substituting aniline in place of 4-aminobenzonitrile to provide a tan solid (yield: 90 mg, 53%). M.p. 154-156 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (br s, 1H), 7.72 (s, 1H), 7.62 (d, J = 18.0 Hz, 2H), 7.19 (d, J = 18.0 Hz, 2H), 7.96-7.82 (m, 3H), 6.61 (d, J = 14.4 Hz, 2H), 4.90 (q, J = 18.0 Hz, 2H), 2.94 (s, 3H). MS (DCI-NH_3) m/z 424 $(M+H)^+$, m/z 441 $(M+NH_4)^+$. Anal. calc. for $C_{19}H_{16}F_3N_3O_3S$: C, 53.90; H, 3.81; N, 9.92. Found: C, 53.87; H, 3.73; N, 9.89.

Example 312

2-(2,2,2-Trifluoroethyl)-4-(2,5-dimethoxyphenylamino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 309 , substituting 2,5-dimethoxyaniline in place of 4-aminobenzonitrile to provide a tan solid (yield: 140 mg, 53%). M.p. 95-96 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (br s, 1H), 7.72 (s, 1H), 7.63 (d, J = 18.0 Hz, 2H), 7.18 (d, J = 18.0 Hz, 2H), 6.54 (d, J = 18.0 Hz, 1H), 6.38 (dd, J = 6.0, 18.0 Hz, 1H), 4.89 (q, J = 18.0 Hz, 2H), 3.73 (s, 3H), 3.47 (s, 3H), 2.96 (s, 3H). MS (DCI-NH_3) m/z 484 $(M+H)^+$, m/z 501 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{20}F_3N_3O_5S$: C, 52.17; H, 4.17; N, 8.69. Found: C, 52.47; H, 4.17; N, 8.43.

Example 313

2-(2,2,2-Trifluoroethyl)-4-(3-fluoroanilino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 309 , substituting 3-fluoroaniline in place of 4-aminobenzonitrile to provide a tan solid (yield: 151.3 mg, 42%). M.p. 156-158 °C. ^{1}H NMR (300 MHz, DMSO) δ 9.18 (s, 1H), 7.91 (s, 1H), 7.62 (d, J = 17.4 Hz, 2H), 7.36 (d, J = 17.4 Hz, 2H), 6.88 (dd, J = 15.0, 15.0 Hz, 1H), 6.56 (m, 1H), 6.49 (m, 2H), 5.04 (q, J = 18.0 Hz, 2H), 3.08 (s, 3H). MS (DCI-NH_3) m/z 442 $(M+H)^+$, m/z 459 $(M+NH_4)^+$, m/z 476 $(M+2NH_4-H)^+$. Anal. calc. for $C_{19}H_{15}F_4N_3O_3S \cdot 0.5\ CH_3COCH_3$: C, 52.33; H, 3.85; N, 8.93. Found: C, 52.51; H, 3.58; N, 8.81.

Example 314

2-(2,2,2-Trifluoroethyl)-4-(2,4-difluoroanilino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 309 , substituting 2,4-difluoroaniline in place of 4-aminobenzonitrile to provide a tan solid (yield: 63.1 mg, 17%). M.p. 170-175 °C. ^{1}H NMR (300 MHz, DMSO) δ 9.00 (s, 1H), 7.80 (s, 1H), 7.57 (d, J = 17.4 Hz, 2H), 7.26 (d, J = 17.4 Hz, 2H), 7.05 (m, 1H), 6.75 (m, 2H), 5.05 (q, J = 18.0 Hz, 2H), 3.09 (s, 3H). MS (DCI-NH_3) m/z 460 $(M+H)^+$, m/z 477 $(M+NH_4)^+$. Anal. calc. for $C_{19}H_{14}F_5N_3O_3S$: C, 49.68; H, 3.07; N, 9.15; found: C, 50.00; H, 2.95; N, 9.10.

Example 315

2-(2,2,2-Trifluoroethyl)-4-(2,3,5-trifluoroanilino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 309, substituting 2,3,5-trifluoroaniline in place of 4-aminobenzonitrile to provide a pale purple solid (yield: 85.3 mg, 22%). M.p. 190-194 °C. ^{1}H NMR (300 MHz, DMSO) δ 9.27 (s, 1H), 7.90 (s, 1H), 7.70 (d, J = 17.4 Hz, 2H), 7.39 (d, J = 17.4 Hz, 2H), 7.03 (m, 1H), 6.76 (m, 1H), 5.06 (q, J = 18.0 Hz, 2H), 3.14 (s, 3H). MS (DCI-NH_3) m/z 495 $(M+NH_4)^+$. Anal. calc. for $C_{19}H_{13}F_6N_3O_3S$: C, 47.80; H, 2.74; N, 8.80. Found: C, 47.51; H, 2.55; N, 8.63.

Example 316

2-(2,2,2-Trifluoroethyl)-4-(4-fluoroanilino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 309, substituting 4-fluoroaniline in place of 4-aminobenzonitrile to provide a tan solid (yield: 15.8 mg, 4%). M.p. 158-160 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (br s, 1H), 7.69 (s, 1H), 7.65 (d, J = 18.0 Hz, 2H), 7.18 (d, J = 18.0 Hz, 2H), 6.63 (d, J = 3.6 Hz, 2H), 6.61 (s, 2H), 4.89 (q, J = 17.4 Hz, 2H), 2.96 (s, 3H). MS (DCI-NH_3) m/z 459 $(M+NH_4)^+$. Anal. calc. for $C_{19}H_{15}F_4N_3O_3S \cdot 1.25\ H_2O$: C, 49.19; H, 3.80; N, 9.05. Found: C, 59.57; H, 3.53; N, 8.70.

Example 317

2-Benzyl-4-(3-thienyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-Benzyl-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone prepared in Example 78 (150 mg, 0.4 mmol), thiophene-3-boronic acid (66.5 mg, 0.52 mmol), CsF (145.8 mg, 0.96 mmol), and tetrakis-(triphenylphosphine)-palladium(0) (13.9 mg, 0.012 mmol) in DME (25 mL) were stirred at reflux for 6 hours TLC (1 CH_2Cl_2:1 hexanes:1.5 ethyl acetate) indicated that all starting materials were consumed. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified using a silica gel column (0.5:2.5:0.5 CH_2Cl_2/hexanes/ethyl acetate). A yellow powder was obtained (yield: 50 mg, 31%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.09 (s, 3H), 5.41 (s, 2H), 6.72 (dd, J = 1.5 Hz, 9 Hz, 1H), 7.13 (dd, J = 3 Hz, 3 Hz, 1H), 7.3-7.45 (m, 5H),

7.5-7.6 (m, 3H), 7.78 (s, 1H), 7.92 (d, 9 Hz, 2H). MS (DCI-NH_3) m/z 423 $(M+H)^+$. Anal. calc. for $C_{22} H_{18}N_2O_3S_2$. 0.5 H_2O: C, 6.23; H, 4.43; N, 6.49. Found C, 61.29; H, 4.40; N, 6.16.

Example 318

2-Benzyl-4-(2-benzofuranyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 317, substituting 2-benzofuranboronic acid 3-thiopheneboronic acid (yield: 46 mg, 25%). ^1H NMR (300 MHz, $CDCl_3$) δ 3.13 (s, 3H), 5.5 (s, 2 H,), 6.85-6.92 (m, 1H), 7.15-7.25 (m, 3H), 7.3-7.42 (m, 3H), 7.45-7.7 (m, 5H), 7.79 (s, 1H) 8.0 (d, J = 9 Hz, 2H), 8.08 (s, 1H). MS (DCI-NH_3), m/z 457 $(M+H)^+$. Anal. calc. for $C_{26}H_{20}N_2O_4S{\cdot}H_2O$: C, 65.80; H, 4.67; N, 5.90. Found C, 65.44; H, 4.42; N, 6.14.

Example 319

2-Benzyl-4-(1,3-dihydro-1-oxo-5-isobenzofuranyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 221 , substituting 2-benzyl-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, prepared in Example 78, in place of 2-(2,2,2-trifluoroethyl)-4-chloro-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone (yield: 112 mg, 44%). M.p. > 250 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 3.20 (s, 3H), 5.34 (s, 2H), 5.36 (s, 2H), 7.30-7.44 (m, 6H), 7.48 (d, J = 8 Hz, 2H), 7.57 (s, 1H), 7.73 (d, J = 8 Hz, 1H), 7.85 (d, J = 8 Hz, 2H), 8.17 (s, 1H). MS (DCI-NH_3) m/z 473 $(M+H)^+$, 490 $(M+NH_4)^+$. Anal. calc. for $C_{26}H_{20}N_2O_5S$: C, 65.46; H, 4.33; N, 5.87. Found: C, 65.56; H, 4.48; N, 5.75.

Example 320

2-Benzyl-4-(5-chloro-2-thienyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 317, substituting 4-chloro-2-thiopheneboronic acid in place of 3-thiopheneboronic acid (yield: 21 mg, 17%). ^1H NMR (300 MHz, $CDCl_3$) δ 3.15 (s, 3H), 5.45 (s, 2H), 6.51 (d, J = 4.5 Hz, 1H), 6.7 (d, J = 4.5 Hz, 1H), 7.3-7.4 (m, 3H), 7.5 = 7.6 (m, 4H), 7.6 (s, 1H), 8.05 (d, J = 9 Hz, 2H). MS (DCI-NH_3), m/z 457 $(M+H)^+$. Anal. calc. for $C_{18}H_{15}ClN_2O_3S$: C, 57.68; H, 4.03; N, 7.47. Found C, 57.61; H, 3.84; N, 7.14.

Example 321

2-Benzyl-4-(3-nitrophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 317, substituting 3-nitrobenzeneboronic acid in place of 3-thiopheneboronic acid (yield: 20 mg, 11%). ^1H NMR (300 MHz, $CDCl_3$) δ 3.0 (s, 3H), 5.93 (s, 2H), 7.6-7.8 (m, 9H), 7.8 (t, J = 4.5 Hz, 3H), 8.04 (s, 1H), 8.15 (m, 1H). MS (DCI-NH_3), m/z 462 $(M+H)^+$. Anal. calc. for $C_{24}H_{19}N_3O_5S$. 0.75 H_2O: C, 60.68; H, 4.35; N, 8.84. Found C, 60.99; H, 3.97; N, 8.35.

Example 322

2-Benzyl-4-(4-vinylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 317, substituting 4-vinylbenzeneboronic acid in place of 3-thiopheneboronic acid (yield: 40 mg, 23%). ^1H NMR (300 MHz, $CDCl_3$) δ 3.05 (s, 3H), 5.28 (d, J = 12 Hz, 1H), 5.41 (s, 2H), 5.74 (d, J = 18 Hz, 1H) 6.65 (dd , J = 12 Hz, 18 Hz, 1H), 7.1-7.6 (m, 11H) 7.83 (d, J = 3 Hz, 2H), 7.85 (s, 1H). MS (DCI-NH_3), m/z 443 $(M+H)^+$. Anal. calc. for $C_{26}H_{22}N_2O_3S$: C, 70.57; H, 5.01; N, 6.33. Found C, 70.34; H, 4.67; N, 5.97.

Example 323

2-Benzyl-4-(4-trifluormethylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 317, substituting 4-(trifluoromethyl)benzeneboronic acid in place of 3-thiopheneboronic acid (yield: 101 mg, 52%). ^1H NMR (300 MHz, $CDCl_3$) δ 3.05 (s, 3H), 5.42 (s, 2H), 7.3-7.5 (m, 8H), 7.55-7.6 m, 3H), 7.85 (s, 2H), 7.9 (s, 1H). MS (DCI-NH_3) m/z 485 $(M+H)^+$. Anal. calc. for $C_{25}H_{19}F_3N_2O_3S \cdot 0.25\ H_2O$: C, 61.40; H, 4.01; N, 5.72. Found C, 61.26; H, 4.01; N, 5.35.

Example 324

2-Benzyl-4-(2-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 317, substituting 2-methoxybenzeneboronic acid in place of 3-thiopheneboronic acid (yield: 75 mg, 42%). ^1H NMR (300 MHz, $CDCl_3$) δ 3.01 (s, 3H), 3.5 (s, 3H), 5.40 (dd, J = 12 Hz, 18 Hz, 2H), 6.76 (d, J = 9 Hz, 1H), 6.85-6.95 (m, 1H), 7.09 (dd, J = 1.5 Hz, 9 Hz, 1H), 7.26-7.41 (m, 6H), 7.55 (dd, J = 1.5 Hz, 9 Hz, 2H), 7.82 (d, J = 9

Hz, 3H). MS (DCI-NH_3) m/z 447 $(M+H)^+$. Anal. calc. for $C_{25}H_{22}N_2O_4S{\cdot}0.5\ H_2O$: C, 65.91; H, 5.08; N, 6.14. Found C, 65.86; H, 5.08; N, 5.58.

Example 325

2-Benzyl-4-(3,4-dimethylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-Benzyl-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (150 mg, 0.4 mmol) prepared in Example 78 was dissolved in anhydrous DME (10 mL) and heated to reflux with 3,4-dimethylbenzeneboronic acid in presence of CsF (146 mg, 0.96 mmol) and tetrakis(triphenylphosphine)palladium (14 mg, 0.012 mmol) for 6 hours. After cooling to room temperature the reaction mixture was diluted with water and extracted with ethyl acetate (100 mL). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo.* The compound was purified on a silica gel column, eluting with 30% ethyl acetate in pentanes, providing the desired compound (yield: 100 mg, 56%). ^1H NMR (300 MHz, $CDCl_3$) δ 2.15, 2.20 (2s, 3H), 2.25, 2.30 (2s, 3H), 3.05, 3.08 (2s, 3H), 5.35, 5.40 (2s, 2H), 6.60-7.1 (m, 3H), 7.30-7.40 (m, 4H), 7.42-7.60 (m, 2H), 7.70-8, 02 (m, 4H). MS (DCI-NH_3) m/z 445 $(M+H)^+$. Anal. calc. for $C_{26}H_{24}N_2O_3S{\cdot}H_2O$: C, 67.51; H, 5.66; N, 6.05. Found: C, 67.45;H, 5.56; N, 5.85.

Example 326

2-Benzyl-4-(3-fluoro-4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 325, substituting 3-fluoro-4-methoxybenzeneboronic acid in place of 3,4-dimethylbenzeneboronic acid (yield: 35 mg, 19%). ^1H NMR (300 MHz, $CDCl_3$) δ 3.05 (s, 3H), 3.85 (s, 3H), 5.3, 5.4 (2s, 2H), 6.75-7.03 (m, 3H), 7.3-7.40 (m, 5H), 7.4-7.55 (dd, J = 1.5 Hz; 7.5 Hz, 2H), 7.8-7.95 (m, 3H). MS (DCI-NH_3) m/z 465 $(M+H)^+$. Anal. calc. for $C_{25}H_{21}N_2O_4S{\cdot}0.25\ H_2O$: C, 64.02; H, 4.62; N, 5.97. Found: C, 63.93; H, 4.54; N, 5.43

Example 327

2-Benzyl-4-[3-(2-methoxypyridyl)]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 325, substituting 2-methoxy-3-pyridylboronic acid in place of 3,4-dimethylbenzeneboronic acid (yield: 35 mg, 19%). ^1H NMR (300 MHz, $CDCl_3$) δ 3.05 (s, 3H), 3.58 (s, 3H), 5.4 (dd, J = 15 Hz, 18 Hz; 2H), 6.88 (m, 1H), 7.28-7.40 (m, 5H), 7.5-7.6 (dd,

J = 1.5 Hz; 7.5 Hz, 3H), 7.82 (s, 1H), 7.85 (d, J = 18 Hz, 2H), 8.15 (br s, 1H). MS (DCI-NH_3) m/z 448 $(M+H)^+$. Anal. calc. for $C_{24}H_{21}N_3O_4S$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.17; H, 5.11; N, 9.04

Example 328

2-Benzyl-4-(3-ethoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 325, substituting 3-ethoxybenzeneboronic acid in place of 3,4-dimethylbenzeneboronic acid (yield: 115 mg, 67%). ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, J = 7.5 Hz, 3H), 3.05 (s, 3H), 3.89 (q, J = 7.5 Hz, 2H), 5.14 (s, 2H), 6.65 (d, J = 9 Hz, 1H), 6.72 (t, J = 1.5 Hz, 1H), 6.8 (dd, J = 1.5 Hz, 9 Hz, 1H), 7.15 (t, J = 9 Hz, 1H), 7.3-7.4 (m, 5H), 7.5-7.6 (m, 2H), 7.85 (d, J = 9 Hz, 3H). MS (DCI-NH_3) m/z 461 $(M+H)^+$. Anal. calc. for $C_{26}H_{24}N_2O_4S \cdot 0.5H_2O$: C, 66.50; H, 5.36; N, 5.96. Found: C, 66.39; H, 5.02; N, 5.77

Example 329

2-Benzyl-4-(4-fluorobenzyl)-5-[4-(methylsulfonyl)phenyl]-(2H)-pyridazinone

329A. 2-Benzyl-4,5-dibromo-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 194A, substituting benzyl hydrazine hydrochloride in place of 4-fluorophenyl hydrazine hydrochloride (yield: 7.86 g, 60%). ^1H NMR (300 MHz, DMSO d_6) δ 5.27 (s, 2H), 7.26-7.41 (m, 5H), 8.19 (s, 1H). MS (DCI-NH_3) m/z 345 $(M+H)^+$, 362 $(M+H)^+$.

329B. 2-Benzyl-5-bromo-4-methoxy-3(2H)-pyridazinone

The title compound was prepared according to the method described in Example 194B, substituting 2-benzyl-4,5-dibromo-3(2H)-pyridazinone for 2-(4-fluorophenyl)-4,5-dibromo-3(2H)-pyridazinone (yield: 2.877 g; 85%). ^1H NMR (300 MHz, DMSO-d_6) δ 4.14 (s, 3H), 5.23 (s, 2H), 7.26-7.38 (m, 5H), 8.11 (s, 1H). MS (DCI-NH_3) m/z 295 $(M+H)^+$, 312 $(M+NH_4)^+$.

329C. 2-Benzyl-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method described in Example 6, substituting 2-benzyl-4-methoxy-5-bromo-3(2H)-pyridazinone for 2-

benzyl-4-methoxy-5-bromo-3(2H)-pyridazinone (yield: 3.705 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.52 (s, 3H), 3.99 (s, 3H), 5.28 (s, 2H), 7.26-7.41 (m, 7H), 7.55 (m, 2H), 8.02 (s, 1H). MS (DCI-NH_3) m/z 339 $(M+H)^+$, 356 $(M+NH_4)^+$.

329D. 2-Benzyl-4-(4-fluorobenzyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 233, substituting 4-fluorobenzyl magnesium chloride in place of cyclohexylmagnesium chloride and 2-benzyl-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone was substituted in place of 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone.

329C. 2-Benzyl-4-methoxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The sulfide compound (Example 329D) was oxidized to the methyl sulfonyl compound according to the method of Example 10. M.p. 186-189 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 3.27 (s, 3H), 3.83 (s, 2H), 5.31 (s, 2H), 6.94-7.05 (m, 4H), 7.27-7.40 (m, 5H), 7.67 (m, 2H), 7.94 (s, 1H), 8.03 (m, 2H). MS (DCI-NH_3) m/z 449 $(M+H)^+$, 466 $(M+NH_4)^+$. Anal. calc. for $C_{25}H_{21}FN_2O_3S$: C, 66.95; H, 4.72; N, 6.25. Found: C, 66.68; H, 4.75; N, 6.14.

Example 330

2-(*tert.*-Butyl)-4-(3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

330A. 2-(*tert.*-Butyl)-4,5-dichloro-3(2H)-pyridazinone

A solution of mucochloric acid (33.8 g, 200 mmol) and *tert.*-butylhydrazine hydrochloride (24.9 g, 200 mmol) in methanol (400 mL) was stirred at reflux overnight. Methanol was removed *in vacuo* and the residue was partitioned between ether and water. The organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel, 100% hexanes). Product-containing fractions were combined and the title compound was crystallized from ether/hexanes (yield: 10.0 g, 22.6%). M.p. 63-64 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65 (s, 9H), 7.73 (s, 1H). MS (DCI-NH_3) m/z 221 $(M+H)^+$, 238 $(M+NH_4)^+$.

330B. 2-(*tert.*-Butyl)-4-(3-methylbutoxy)-5-chloro-3(2H)-pyridazinone

A stirred, room temperature solution of 3-methyl-1-butanol (0.5 mL, 4.52 mmol) in tetrahydrofuran (10 mL) was treated with a 60% oil suspension of sodium hydride (0.24 g, 5.88 mmol). After 5 minutes, hydrogen gas evolution had subsided, so the dichloro-intermediate from Example 330A (1.0 g, 4.52 mmol) was

added and the reaction mixture was stirred at room temperature for 20 hours. The reaction was quenched with 10% aqueous citric acid and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo,* and the residue was purified by column chromatography (silica gel, 100% hexanes). The title compound was obtained as a pale yellow oil (yield: 0.7 g, 56.7%). ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (d, J = 6 Hz, 6H), 1.63 (s, 9H), 1.64 (q, J = 6 Hz, 2H), 1.85 (nonet, J = 6 Hz, 1H), 4.49 (t, J = 6 Hz, 2H), 7.64 (s, 1H). MS (DCI-NH_3) m/z 273 $(M+H)^+$, 290 $(M+NH_4)^+$.

330C. <u>2-(*tert*.-Butyl)-4-(3-methylbutoxy)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone</u>

A solution of the intermediate from Example 330B (700 mg, 2.57 mmol), 4-(methylthio)benzeneboronic acid (560 mg, 3.34 mmol), cesium carbonate (2.17 g, 6.67 mmol), and tetrakis(triphenylphosphine)palladium(0) (210 mg, 0.18 mmol) in dimethoxyethane (40 mL) was heated at reflux for 5 hours. The heat source was then removed and the reaction mixture was stirred at room temperature for 64 hours. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* to provide a brown oil. This oil was purified by column chromatography twice (silica gel, 97:3 hexanes/ethyl acetate, then 96:4 hexanes/ethyl acetate) to provide a semi-solid product (yield: 270 mg, 29.2%). ^1H NMR (300 MHz, $CDCl_3$) δ 0.81 (d, J = 6 Hz, 6H), 1.49 (q, J = 6 Hz, 2H), 1.63 (nonet, J = 6 Hz, 1H), 1.69 (s, 9H), 2.52 (s, 3H), 7.32 (d, J = 9 Hz, 2H), 7.50 (d, J = 9 Hz, 2H), 7.73 (s, 1H). MS (DCI) m/z 361 $(M+H)^+$.

330D. <u>2-(*tert*.-Butyl)-4-(3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone</u>

The title compound was prepared according to the method of Example 10, substituting 2-(*tert*.-butyl)-4-(3-methylbutoxy)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone for 4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (yield: 188 mg, 63.9%). M.p. 138-139°C. ^1H NMR (300 MHz, $CDCl_3$) δ 0.81 (d, J = 6 Hz, 2H), 1.48 (q, J = 6 Hz, 2H), 1.48-1.68 (m, 1H), 1.69 (s, 9H), 3.10 (s, 3H), 4.38 (t, J = 6 Hz, 2H), 7.71 (s, 1H), 7.74 (d, J = 9 Hz, 2H), 8.03 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 393 $(M+H)^+$. Anal. calc. for $C_{20}H_{28}N_2O_4S$: C, 61.20; H, 7.19; N, 7.14. Found: C, 61.13; H, 7.23; N, 6.89.

Example 331

2-(3-Chlorophenyl)-4-methoxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 10, substituting 2-(3-chlorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (Example 207C) in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (yield: 3.31 g, 96%). M.p. 112-114 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 3.31 (m, 3H), 4.10 (m, 3H), 7.52-7.65 (m, 3H), 7.75 (m, 1H), 7.90 (m, 2H), 8.07 (m, 2H), 8.21 (s, 1H). MS (DCI-NH_3) m/z 391 $(M+H)^+$, 408 $(M+NH_4)^+$. Anal. calc. for: $C_{18}H_{15}ClN_2O_4S{\cdot}0.25\ H_2O$: C, 54.68; H, 3.95; N, 7.08. Found: C, 54.59; H, 3.65; N, 6.98.

Example 332

2-(3-Chlorophenyl)-4-hydroxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A suspension of 2-(3-chlorophenyl)-4-(methoxy)-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone (6.26 g, 16 mmol) in 5% NaOH (54 mL) dioxane (39.4 mL) was heated at reflux and stirred for 1.5 hours. As the reaction proceeds, the solution becomes orange and homogeneous. The mixture was cooled and poured into 1N HCl, with constant stirring. The resulting white solid was filtered and rinsed with H_2O and left to dry overnight. The mostly dry product was taken up in CH_2Cl_2 and azeotroped with toluene to remove any remaining H_2O, to provide the desired product as a white solid (yield: 6.79 g, >100%). ^{1}H NMR (300 MHz, DMSO d_6) δ 2.27 (s, 3H), 7.51-7.62 (m, 2H), 7.68 (m, 1H), 7.79 (m, 1H), 8.03 (m, 4H), 8.24 (s, 1H). MS (DCI-NH_3) m/z 377 $(M+H)^+$, 396 $(M+NH_4)^+$.

Example 333

2-(3-Chlorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

To a 0 °C solution of 2-(3-chlorophenyl)-4-hydroxy-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone, prepared in Example 332, (6.79 g, 16 mmol) in pyridine (160 mL) was added p-toluenesulfonyl chloride (3.06 g, 16 mmol). The solution was left to warm slowly to room temperature with stirring under nitrogen. After 2.5 hours, the mixture was poured into H_2O with constant stirring. The resulting off-white solid was filtered, rinsed with H_2O and dried to provide the desired product (yield: 6.26 g, 79%). M.p. 198-200 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 2.35 (s, 3H), 3.28 (s, 3H), 7.20 (m, 2H), 7.52-7.64 (M, 5H), 7.70 (m, 3H), 7.89 (m, 2H), 8.32 (s, 1H). MS APCI+ 531 $(M+H)^+$, 548 $(M+H_2O)^+$, APCI$^-$493 $(M+35)^-$.

Anal. calc. for $C_{24}H_{19}ClN_2O_6S_2$: C, 54.29; H, 3.61; N, 5.28. Found: C, 54.55; H, 3.46; N, 5.57.

Example 334

2-(3-Chlorophenyl)-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A solution of 2-(3-chlorophenyl)-4-hydroxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, prepared in Example 332, in $POCl_3$ was heated to reflux for 3 hours while stirring under nitrogen. The mixture was cooled to room temperature and poured into ice with constant swirling. The resulting white solid was extracted with ethyl acetate. The combined organics were washed with H_2O, dried over $MgSO_4$, and concentrated to a solid. The crude product was purified using flash chromatography (SiO_2, eluting with 1:1 ethyl acetate/hexanes) to provide the desired product (yield: 0.151 g, 29%). M.p. 203-204 °C. ^1H NMR (300 MHz, DMSO d_6) δ 3.29-3.36 (3H, obstructed by H_2O), 7.60 (m, 3H), 7.76 (m, 1H), 7.92 (m, 2H), 8.14 (m, 2H), 8.25 (s, 1H). MS (DCI-NH_3) m/z 395 $(M+H)^+$, 412 $(M+NH_4)^+$. Anal. calc. for $C_{17}H_{12}Cl_2N_2O_3S$: C, 51.66; H, 3.06; N, 7.09. Found: C, 51.67; H, 3.03; N, 6.93.

Example 335

2-(3-Chlorophenyl)-4-(2-methylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

To a stirred suspension of 2-(3-chlorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, prepared in Example 333, (0.175 g, 0.33 mmol) in THF (3.3 mL) was added isobutanol (0.03 mL, 0.33 mmol), and NaH (0.0132 g, 0.33 mmol). The resulting solution was stirred under nitrogen for 1 hour. The reaction was poured into H_2O and extracted with ethyl acetate. The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. The crude solid was purified using flash chromatography (SiO_2, 2:1 hexanes:ethyl acetate) to provide the desired product (yield: 0.1088 g 76%). M.p. 166-169 °C. ^1H NMR (300 MHz, DMSO d_6) δ 0.78 (d, J = 6 Hz, 6H), 1.84 (m, 1H), 3.29 (s, 3H), 4.20 (d, J = 6 Hz, 2H), 7.51-7.63 (m, 3H), 7.76 (m, 1H), 7.92 (m, 2H), 8.07 (m, 2H), 8.21 (s, 1H). MS (DCI-NH_3) m/z 433 $(M+H)^+$, 450 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{21}ClN_2O_4S$: C, 57.07; H, 5.01; N, 6.33. Found: C, 57.06; H, 4.78; N, 6.13.

Example 336

2-(3-Chlorophenyl)-4-(*t*-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting *t*-butanol in place of isobutanol (yield: 0.093 g, 66%). M.p. 232-235 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 1.18 (s, 9H), 3.30 (s, 3H), 7.52-7.64 (m, 3H), 7.74 (m, 1H), 7.92 (m, 2H), 8.08 (m, 2H), 8.20 (s, 1H). MS (DCI-NH_3) m/z 433 $(M+H)^+$, 450 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{21}ClN_2O_4S$: C, 58.26; H, 4.89; N, 6.47. Found: C, 58.21; H, 4.88; N, 6.28.

Example 337

2-(3-Chlorophenyl)-4-(cyclohexyloxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting cyclohexanol in place of isobutanol (yield: 0.139 g, 92%). semi-solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09-1.50 (m, 6H), 1.57 (m, 2H), 1.88 (m, 2H), 3.13 (s, 3H), 5.19 (m, 1H), 7.38-7.48 (m, 2H), 7.59 (m, 1H), 7.70 (m, 1H), 7.83 (m, 2H), 7.92 (s, 1H), 8.07 (m, 2H). MS APCI+ 459 $(M+H)^+$, 476 $(M+H_2O)^+$, APCI$^-$458 $(M)^-$, 493 $(M+35)^-$. Anal. calc. for $C_{23}H_{23}ClN_2O_4S{\cdot}0.25\ H_2O$: C, 59.60; H, 5.11; N, 6.04. Found: C, 59.48; H, 4.86; N, 5.88.

Example 338

2-(3-Chlorophenyl)-4-(2,2-dimethylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting neopentyl alcohol in place of isobutanol (yield: 0.109 g, 74%). M.p. 151-153 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 0.78 (s, 9H), 3.29 (s, 3H), 4.10 (s, 2H), 7.52-7.64 (m, 3H), 7.76 (m, 1H), 7.92 (m, 2H), 8.07 (m, 2H), 8.20 (s, 1H). MS (DCI-NH_3) m/z 447 $(M+H)^+$, 464 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{23}ClN_2O_4S$: C, 59.12; H, 5.19; N, 6.27. Found C, 59.40; H, 5.31; N, 5.99.

Example 339

2-(3-Chlorophenyl)-4-(3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 3-methyl-1-butanol was substituted in place of isobutanol (yield: 0.229 g, 80.5%). M.p. 134-135 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 0.79 (d, J = 6 Hz, 6H), 1.42-1.64 (m, 3H), 3.30 (s, 3H), 4.43 (t, J = 6 Hz, 2H), 7.52-7.65 (m, 3H), 7.76

(m, 1H), 7.90 (m, 2H), 8.07 (m, 2H), 8.21 (s, 1H). MS (DCI-NH_3) m/z 447 $(M+H)^+$, 464 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{23}ClN_2O_4S$: c, 59.12; H, 5.19; N, 6.27. Found: C, 58.91; H, 5.12; N, 6.01.

Example 340

2-(3-Chlorophenyl)-4-(3-octyn-1-yloxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 3-octyn-1-ol in place of isobutanol (yield: 0.128 g, 77%). Oil. ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (m, 3H), 1.25-1.44 (m, 4H), 2.05 (m, 2H), 2.52 (m, 2H), 4.68 (t, J = 6 Hz, 2H), 7.43 (m, 2H), 7.59 (m, 1H), 7.70 (m, 1H), 7.86 (m, 2H), 7.92 (s, 1H). MS (DCI-NH_3) m/z 485 $(M+H)^+$. Anal. calc. for $C_{25}H_{25}ClN_2O_4S$: C, 61.94; H, 5.20; N, 5.78. Found: C, 61.82; H, 4.99; N, 5.57.

Example 341

2-(3-Chlorophenyl)-4-[2-(dimethylamino)ethoxy]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting N,N-(dimethyl)ethanolamine in place of isobutanol (yield: 0.111 g, 75%). M.p. 110-113 °C. ^1H NMR (300 MHz, DMSO d_6) δ 2.29 (bs, 6H), 2.68 (bs, 2H), 4.68 (t, J = 5 Hz, 2H), 7.38-7.48 (m, 2H), 7.57 (m, 1H), 7.68 (m, 1H), 7.89 (m, 2H), 8.07 (m, 2H). MS (DCI-NH_3) m/z 448 $(M+H)^+$. Anal. calc. for $C_{21}H_{22}ClN_3O_4S \cdot 0.50\ H_2O$: C, 55.19; H, 5.07; N, 9.19. Found: C, 55.24; H, 4.97; N, 9.07.

Example 342

2-(3-Chlorophenyl)-4-[2-methyl-1-(1-methylethyl)propoxy]-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 2,4-dimethyl-3-pentanol in place of isobutanol (yield: 0.075 g, 48%). Semi-solid; ^1H NMR (300 MHz, DMSO d_6) δ 0.79 (m, 12H), 1.78-1.92 (m, J = 6 Hz, 2H), 3.29 (s, 3H), 5.40 (t, J = 6 Hz, 1H), 7.57 (m, 3H), 7.72 (m, 1H), 7.91 (m, 2H), 8.07 (m, 2H), 8.17 (m, 1H). MS (DCI-NH_3) m/z 475 $(M+H)^+$, 492 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{27}ClN_2O_4S$ (0.75 H_2O): C, 59.00; H, 5.88; N, 5.78. Found: C, 58.83; H, 5.74; N, 5.52.

Example 343

2-(3-Chlorophenyl)-4-(phenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting phenol in place of isobutanol (yield: 0.053 g, 35%). M.p. 205-207 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 3.28 (s, 3H), 7.08 (m, 3H), 7.31 (m 2H), 7.50-7.64 (m, 3H), 7.73 (m, 1H), 7.90 (m, 2H), 8.05 (m, 2H), 8.40 (s, 1H). MS (DCI-NH_3) m/z 453 $(M+H)^+$, 470 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{17}ClN_2O_4S$: C, 60.99; H, 3.78; N, 6.19. Found: C, 60.79; H, 3.65; N, 5.87.

Example 344

2-(3-Chlorophenyl)-4-[3-(dimethylamino)phenyl]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 3-(dimethylamino)phenol in place of isobutanol (yield: 0.057 g, 60%). M.p. 191-193; ^{1}H NMR (300 MHz, DMSO d_6) δ 2.85 (s, 6H), 3.27 (s, 3H), 6.36 (m, 3H), 7.05 (m, 1H), 7.51-7.63 (m, 3H), 7.72 (m, 1H), 7.90 (m, 2H), 8.05 (m, 2H), 8.39 (s, 1H). MS APCI+ 495 $(M+H)^+$, APCI$^-$, 495 $(M)^-$, 590 $(M+35)^-$. Anal. calc. for $C_{25}H_{22}ClN_3O_4S$: C, 60.54; H, 4.47; N, 8.47. Found: C, 60.04; H, 4.49; N, 8.26.

Example 345

2-(3-Chlorophenyl)-4-(4-methoxyphenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 4-methoxyphenol in place of isobutanol (yield: 0.080 g, 69%). M.p. 182-184 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 3.27 (s, 3H), 3.70 (s, 3H), 6.84 (m, 2H), 7.00 (m, 2H), 7.56 (m, 3H), 7.72 (m, 1H), 7.90 (m, 2H), 8.04 (m, 2H), 8.38 (s, 1H). MS (DCI-NH_3) m/z 483 $(M+H)^+$, 500 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{19}ClN_2O_5S$: C, 59.64; H, 3.97; N, 5.80. Found: C, 59.86; H, 3.94; N, 5.62.

Example 346

2-(3,4-Difluorophenyl)-4-(2-methylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 2-(3,4-difluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(3-chlorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone (yield: 150 mg, 61%) . M.p. 116-117 °C. ^{1}H NMR (300

MHz, DMSO-d_6) δ 0.78 (d, 6H), 1.84, (m, 1H), 3.3 (s, 3H), 4.2 (d, 2H), 7.54 (m, 1H), 7.6 (m, 1H), 7.82 (m, 1H), 7.91 (d, 2H), 8.07 (d, 2H), 8.21 (s, 1H). MS (DCI-NH_3) m/z 435 $(M+H)^+$, 452 $(M+NH_4)^+$. Anal. calc. for $C_{21}F_2H_{20}N_2O_4S$: C, 58.06; H, 4.64; N, 6.45.

Example 347

2-(3,4-Difluorophenyl)-4-(3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 346 substituting 3-methyl-1-butanol in place of isobutanol (yield: 63 mg, 23%). M.p. 121-123 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 0.78 (d, 6H), 1.48, (m, 3H), 3.3 (s, 3H), 4.43 (t, 2H), 7.54 (m, 1H), 7.6 (m, 1H), 7.82 (m, 1H), 7.91 (d, J = 9 Hz, 2H), 8.07 (d, J = 9 Hz, 2H), 8.2 (s, 1H). MS (DCI-NH_3) m/z 449 $(M+H)^+$, 466 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{22}F_2N_2O_4S$: C, 58.92; H, 4.94; N, 6.25. Found, C, 59.22; H, 4.97; N, 6.07.

Example 348

2-(3,4-Difluorophenyl)-4-(4-fluorophenoxy)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 346, starting with 2-(3,4-difluorophenyl)-4-tosyloxy-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(3-difluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting 4-fluorophenol in place of isobutanol M.p. 168-170 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 3.39 (s, 3H), 7.15 (d, 4H), 7.51 (m, 1H), 7.6 (m, 1H) 7.75 (m, 3H), 7.97 (t, 1H); 8.4 (s, 1H). MS (DCI-NH_3) m/z 491 $(M+H)^+$, 508 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{14}F_4N_2O_4S$: C, 56.33; H, 2.88; N, 5.71. Found, C, 56.07; H, 2.94; N, 5.33.

Example 349

2-(3,4-Difluorophenyl)-4-(2,2-dimethylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 346 substituting neopentyl alcohol in place of isobutanol (yield: 1.18 g, 94%). M.p. 126-128 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 0.78 (s, 9H), 3.3 (s, 3H), 4.1 (s, 2H), 7.51 (m, 1H), 7.6 (m, 1H), 7.82 (m, 1H), 7.91 (d, J = 9 Hz, 2H), 8.07 (d, J = 9 Hz, 2H), 8.21

(s, 1H). MS (DCI-NH_3) m/z 449 $(M+H)^+$, 466 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{22}F_2N_2O_4S$: C, 58.92; H, 4.94; N, 6.25. Found: C, 59.03; H, 5.03; N, 6.18.

Example 350

2-(3,4-Difluorophenyl)-4-[2-(isopropoxy)ethoxy]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 346 substituting 2-(isopropoxy)ethanol in place of isobutanol (yield: 432 mg, 72%). M.p. 105-107 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 0.95 (d, 6H), 3.3 (s, 3H), 3.43 (m, 1H), 3.54 (m, 2H), 4.63 (m, 2H), 7.54 (m, 1H), 7.6 (m, 1H), 7.8 (m, 1H), 8.01 (m, 4H), 8.2 (s, 1H). MS (DCI-NH_3) m/z 465 $(M+H)^+$, 482 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{22}F_2N_2O_5S$: C, 56.89; H, 4.77; N, 6.03. Found, C, 57.03; H, 4.65; N, 5.83.

Example 351

2-(3,4-Difluorophenyl)-4-(3-methylpentyloxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 346 substituting 3-methylpentyl-1-ol in place of isobutanol (yield: 400 mg, 80%). M.p. 100-102 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 0.75 (m, 6H), 1.05 (m, 1H), 1.28 (m, 3H) 1.6 (m, 1H), 3.3 (s, 3H), 4.45 (m, 2H), 7.5 (m, 1H), 7.6 (m, 1H), 7.8 (m, 1H), 7.9 (d, J = 9 Hz, 2H) 8.05 (d, J = 9 Hz, 2H), 8.2 (s, 1H). MS (DCI-NH_3) m/z 463 $(M+H)^+$, 480 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{24}F_2N_2O_4S$: C, 59.73; H, 5.23; N, 6.06. Found, C, 59.78; H, 5.31; N, 6.00.

Example 352

2-(3,4-Difluorophenyl)-4-(4-methyl-3-penten-1-yloxy)-5-[4-(methylsulfonyl)phenyl]-5-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 346 substituting 4-methyl-3-pentene-1-ol in place of isobutanol (yield: 405 mg, 67.8%). M.p. 88-90 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 1.5 (d, 6H), 2.27 (m, 2H) 3.3 (s, 3H), 4.43 (t, 2H), 4.95 (m, 1H), 7.5 (m, 1H), 7.6 (m, 1H), 7.8 (m, 1H), 7.9 (d, 2H), 8.06 (d, 2H), 8.2 (s, 1H). MS (DCI-NH_3) m/z 461 $(M+H)^+$, 478 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{22}F_2N_2O_4S$: C, 59.99; H, 4.82; N, 6.08. Found, C, 59.88; H, 4.76; N, 5.84.

Example 353

2-(3,4-Difluorophenyl)-4-[3-(methoxy)butoxy]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 346 substituting 3-methoxybutyl-1-ol in place of isobutanol (yield: 350 mg, 68%) . M.p. 99-101 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.97 (d, 3H), 1.7 (m, 2H), 3.05 (s, 3H), 3.2 (m, 1H) 3.3 (s, 3H), 4.45 (m, 2H), 7.54 (m, 1H), 7.6 (m, 1H), 7.8 (m, 1H), 7.9 (d, J = 9 Hz, 2H) 8.01 (d, J = 9 Hz, 2H), 8.2 (s, 1H). MS (DCI-NH_3) m/z 465 $(M+H)^+$, 482 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{22}F_2N_2O_5S$: C, 56.89; H, 4.77; N, 6.03. Found, C, 56.60; H, 4.83; N, 5.96.

Example 354

2-(3-Chlorophenyl)-4-(*N*-methylbenzylamino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone:

To a rapidly stirred 0 °C mixture of *N*-methylbenzylamine (67.5 mg, 0.56 mmol) and tetrahydrofuran (3.7 mL) was slowly added dropwise an n-BuLi solution (0.235 mL, 0.59 mmol, 2.5 M in hexanes). The reaction mixture was stirred for 10 minutes at 0 °C and 1 hour at 23 °C. The solution was cooled to -78 °C, and a tetrahydrofuran (10-15 mL) solution of the 2-(3-chlorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (200 mg, 0.56 mmol) slowly added along the interior wall of the reaction vessel. This reaction mixture was stirred overnight, slowly warming to 23 °C as the cooling bath evaporated. The reaction was quenched with water and diluted with a large excess of ethyl acetate. The layers were separated, and the ethyl acetate layer washed with additional water and brine and dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was chromatographed (flash silica gel, ethyl acetate/hexanes 1:9) to provide 2-(3-chlorophenyl)-4-(*N*-methyl benzylamino)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (yield: 145 mg, 58%).

The title compound was prepared according to the method of Example 10, substituting 2-(3-chlorophenyl)-4-(*N*-methylbenzylamino)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylthio)-phenyl]-3(2H)-pyridazinone (yield: 143 mg, 95%). M.p. 60-85 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (s, 3H), 3.09 (s, 3H), 4.63 (s, 2H), 7.19 (d, J = 8.7 Hz, 2H), 7.24-7.29 (m, 2H), 7.32-7.48 (m, 5H), 7.60 (ddd, J = 7.2, 1.8, 1.8 Hz, 1H), 7.67 (s, 1H), 7.70 (dd, J = 1.8, 1.8 Hz, 1H), 7.91 (d, J = 8.7 Hz, 2H). MS (APCI+) m/z 480 $(M+H)^+$.

Example 355

2-(4-Fluorophenyl)-4-(1-piperidinyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

To a slightly heterogeneous solution of piperidine (99.7 mg, 1.17 mmol) and toluene (8 mL) cooled to -78 °C was slowly added dropwise an *n*-BuLi solution (0.235 mL, 0.59 mmol, 2.5 M in hexanes). After stirring at -78 °C for 10 minutes, the cooling bath was removed and the mixture stirred an additional 1 hour at 23 °C. The 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (400 mg, 1.17 mmol) was dissolved in portions in toluene (3 x 6-7 mL aliquots) with a heat gun and cooled to 0 °C prior to transfer via syringe to the lithium amide solution (cooled to -78 °C). The addition was made slowly along the interior wall of the reaction vessel. This reaction mixture was stirred overnight, slowly warming to 23 °C as the cooling bath evaporated. The reaction was quenched with water and diluted with a large excess of ethyl acetate. The layers were separated, and the ethyl acetate layer washed with additional water and brine and dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was chromatographed (flash silica gel, ethyl acetate/hexanes 1:2) to provide 440 mg (95%) of 2-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-4-piperidino-3(2H)-pyridazinone.

The title compound was prepared according to the method of Example 10, substituting 2-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-4-piperidino-3(2H)-pyridazinone in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (yield: 165 mg, 98%). M.p. 80-100 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.59 (br s, 6H), 2.59 (br s, 4H), 3.14 (s, 3H), 7.17 (dd, J = 8.7, 8.7 Hz, 2H), 7.51 (d, J = 8.7 Hz, 2H), 7.55-7.62 (m, 2H), 7.68 (s, 1H), 8.06 (d, J = 8.7 Hz, 2H). MS (APCI+) m/z 428 $(M+H)^+$. Powdered out in CH_2Cl_2/C_6H_{14}. Anal. calc. for $C_{22}H_{22}FN_3O_3S{\cdot}0.25C_6H_{14}$: C, 62.85; H, 5.72; N, 9.35. Found: C, 62.46; H, 5.77; N, 9.13.

Example 356

2-(4-Fluorophenyl)-4-(1-pyrrolidinyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 355, substituting pyrrolidine for piperidine (yield: 107 mg, 82%). M.p. 192-195 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.71-1.80 (m, 4H), 3.13 (s, 3H), 3.40-3.49 (m, 4H), 7.16 (dd, J = 8.7, 8.7 Hz, 2H), 7.47-7.60 (m, 5H), 7.99 (d, J = 8.7 Hz, 2H). MS (APCI+)

m/z 414 $(M+H)^+$. Anal. calc. for $C_{21}H_{20}FN_3O_3S$: C, 61.00; H, 4.87; N, 10.16. Found: C, 60.95; H, 4.94; N, 10.07.

Example 357

2-(3-Chlorophenyl)-4-(4-methylphenylthio)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

To a stirred suspension of 2-(3-chlorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, prepared in Example 333, (0.0802 g, 0.15 mmol) in EtOH (1.5 mL) was added thiocresol (0.019 g, 0.15 mmol) and K_2CO_3 (0.0203 g, 0.15 mmol). The suspension was heated to 50 °C with stirring for 2.5 hours. The mixture was poured into H_2O with constant stirring. The resulting precipitate was filtered, rinsed with H_2O and dried to provide the desired product (yield: 0.060 g, 83%). M.p. 178-178 °C. ^1H NMR (300 MHz, DMSO d_6) δ 2.19 (s, 3H), 3.23 (s, 3H), 6.95 (m, 2H), 7.08 (m, 2H), 7.52-7.66 (m, 3H), 7.72 (m, 1H), 7.88 (m, 2H), 8.08 (s, 1H). MS (DCI-NH_3) m/z 483 $(M+H)^+$, 500 $(M+NH_4)^+$. Anal. calc. for: $C_{24}H_{19}ClN_2O_3S_2 \cdot 0.75\ H_2O$: C, 58.05; H, 4.16; N, 5.64. Found: C, 57.99; H, 3.69; N, 5.76.

Example 358

2-(3-Chlorophenyl)-4-(2-pyridylthio)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 357, substituting 2-mercaptopyridine in place of thiocresol (yield: 0.061 g, 39%). M.p. 110-114 °C. ^1H NMR (300 MHz, DMSO d_6) δ 3.28 (s, 3H), 7.16 (m, 1H), 7.37 (m, 1H), 7.51-7.71 (m, 5H), 7.81 (m, 2H), 8.03 (m, 2H), 8.27 (s, 1H), 8.34 (m, 1H). MS (DCI-NH_3) m/z 470 $(M+H)^+$. Anal. calc. for $C_{22}H_{16}ClN_3O_3S_2 \cdot 0.50\ H_2O$: C, 55.16; H, 3.57; N, 8.77. Found: C, 54.88; H, 3.19; N, 8.59.

Example 359

2-(3-Chlorophenyl)-4-(phenylmethylthio)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

To a stirred suspension of 2-(3-chlorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, prepared in Example 333, (0.175 g, 0.33 mmol) in THF (3.3 mL) was added benzyl mercaptan (0.04 mL, 0.33 mmol) and TEA (0.046 mL, 0.33 mmol). The resulting solution was stirred at room temperature under nitrogen for 1 hour. The mixture was poured into H_2O and extracted with

ethyl acetate. The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude product was purified using flash chromatography (SiO_2, 2:1 hexanes:ethyl acetate) to provide the desired product (yield: 0.136 g 85%). M.p. 142-145 °C. ^1H NMR (300 MHz, DMSO d_6) δ 3.31 (s, 3H), 4.36 (s, 2H), 7.17 (m, 2H), 7.21-7.33 (m, 3H), 7.51 (m, 2H), 7.57-7.64 (m, 3H), 7.74 (m, 1H), 8.01 (m, 2H). MS (DCI-NH_3) m/z 483 $(M+H)^+$, 500 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{19}ClN_2O_3S_2$: C, 59.68; H, 3.96; N, 5.80. Found: C, 59.40; H, 4.11; N, 5.71.

Example 360

2-(3-Chlorophenyl)-4-(2-furylmethylthio)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 359, substituting furfuryl mercaptan in place of benzyl mercaptan (yield: 0.162 g, 100%). M.p. 140-149 °C. ^1H NMR (300 MHz, DMSO d_6) δ 3.31 (s, 3H), 4.46 (s, 2H), 6.20 (m, 1H), 6.37 (m, 1H), 7.50-7.67 (m, 6H), 7.77 (m, 1H), 8.03 (m, 2H), 8.08 (s, 1H). MS (DCI-NH_3) m/z 473 $(M+H)^+$, 490 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{17}ClN_2O_4S_2$: C, 55.87; H, 3.62; N, 5.92. Found: C, 55.84; H, 3.61; N, 5.82.

Example 361

2-(3-Chlorophenyl)-4-]2-(methylpropyl)thio]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 359, substituting 2-methyl-1-propanethiol in place of benzyl mercaptan (yield: 0.134 g, 91%). Oil. ^1H NMR (300 MHz, DMSO d_6) δ 0.61 (d, J = 6 Hz, 6H), 1.54-1.69 (m, 1H), 2.91 (d, J = 6 Hz, 2H), 3.33 (s, 3H), 7.52-7.64 (m, 3H), 7.74 (m, 1H), 7.79 (m, 2H), 8.04 (m, 3H). MS (DCI-NH_3) m/z 449 $(M+H)^+$, 466 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{21}ClN_2O_3S_2$ (0.50 H_20): C, 55.07; H, 4.84; N, 6.11. Found: C, 54.70; H, 4.64; N, 5.85.

Example 362

2-(3-Chlorophenyl)-4-(cyclopentyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

To a -78 °C solution of 2-(3-chlorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone, prepared in Example 333, (0.175 g, 0.33 mmol) in THF (3.3 mL) was added cyclopentyl magnesium chloride (0.17 mL, 1.0 M in diethyl ether). The resulting solution was stirred under nitrogen less than 1hour with

warming to room temperature. The reaction was poured into water and extracted with ethyl acetate. The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude product was purified using flash chromatography (SiO_2, 2:1 ethyl acetate:hexanes) to provide the desired product (yield: 0.1328 g, 94%). M.p. 155-157 °C. ^1H NMR (300 MHz, DMSO d_6) δ 1.50 (m, 2H), 1.66 (m, 2H), 1.79 (m, 2H), 2.09 (m, 2H), 2.90 (m, J = 8 Hz, 1H), 3.26-3.37 (3H, obstructed by H_2O), 7.49-7.63 (m, 3H), 7.71 (m, 3H), 7.97 (s, 1H), 8.10 (m, 2H). MS ($DCI-NH_3$) m/z 429 $(M+H)^+$, 446 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{21}ClN_2O_3S$: C, 61.60; H, 4.93; N, 6.53. Found: C, 61.48; H, 4.81; N, 6.22.

Example 363

2-(3-Chlorophenyl)-4-(3-methylpropyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound, an oil, was prepared according to the method of Example 362, substituting isobutyl magnesium chloride in place of cyclohexylmagnesium chloride, (yield: 0.132 g, 96%). ^1H NMR (300 MHz, $CDCl_3$) δ 0.77 (d, J = 6 Hz, 6H), 2.08 (m, 1H), 2.54 (d, J = 7 Hz, 2H), 7.36-7.46 (m, 2H), 7.56 (m, 2H), 7.62 (m, 1H), 7.73 (m, 2H), 8.11 (m, 2H). MS ($DCI-NH_3$) m/z 417 $(M+H)^+$, 434 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{21}ClN_2O_3S \cdot 0.50\ H_2O$: C, 59.21; H, 5.20; N, 6.57. Found: C, 59.27; H, 5.40; N, 6.12.

Example 364

2-(3-Chlorophenyl)-4-(cyclohexylmethyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound, an oil, was prepared according to the method of Example 362, substituting cyclohexylmethyl magnesium bromide in place of cyclopentyl magnesium chloride (yield: 0.0579 g, 38%). ^1H NMR (300 MHz, DMSO d_6) δ 0.66 (m, 2H), 1.03 (m, 3H), 1.50 (m, 6H), 1.61 (m, 1H), 2.46 (m, 1H), 3.27-3.42 (3H, obstructed by H_2O), 7.50-7.66 (m, 3H), 7.75 (m, 3H), 7.99 (s, 1H), 8.10 (m, 2H). MS ($DCI-NH_3$) m/z 457 $(M+H)^+$, 474 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{25}ClN_2O_3S$: C, 63.08; H, 5.51; N, 6.13. Found: C, 63.08; H, 5.47; N, 6.04.

Example 365

2-(3-Chlorophenyl)-4-(2-cyclohexylethyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 362, substituting cyclohexylethyl magnesium bromide in place of cyclopentyl magnesium chloride (yield: 0.165 g, 94%). ^{1}H NMR (300 MHz, DMSO d_6) δ 0.76 (m, 3H), 0.99-1.21 (m, 5H), 1.31-1.62 (m, 8H), 2.42-2.56 (1H, obstructed by DMSO), 3.25-3.34 (2H, obstructed by H_2O), 7.48-7.65 (m, 3H), 7.48-7.65 (m, 3H), 7.76 (m, 3H), 8.01 (s, 1H), 8.10 (m, 2H). MS (DCI-NH_3) m/z 471 $(M+H)^+$, 488 $(M+NH_4)^+$. Anal. calc. for $C_{25}H_{27}ClN_2O_3S$: C, 63.75; H, 5.78; N, 5.95. Found: C, 63.48; H, 5.70; N, 5.67.

Example 366

2-(3-Chlorophenyl)-4-(3-methylbutyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 362, substituting 3-methylbutyl magnesium bromide in place of cyclohexylmagnesium chloride (yield: 0.0221 g, 16%). M.p. 60-65 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 0.75 (d, J = 7 Hz, 6H), 1.32-1.52 (m, 3H), 3.31 (s, 3H), 7.50-7.65 (m, 3H), 7.77 (m, 3H), 8.03 (s, 1H), 8.11 (m, 2H). MS (DCI-NH_3) m/z 431 $(M+H)^+$, 448 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{23}ClN_2O_3S \cdot 0.25\ H_2O$: C, 60.68; H, 5.43; H, 6.43. Found C, 60.29; H, 5.60; N, 6.17.

Example 367

2-(3-Chlorophenyl)-4-benzyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 362, substituting benzyl magnesium chloride in place of cyclohexylmagnesium chloride. M.p. 174-177 °C (yield: 25.9 g, 57%). ^{1}H NMR (300 MHz, DMSO d_6) δ 3.30 (s, 3H), 3.91 (bs, 2H), 7.02 (m, 2H), 7.12-7.25 (m, 3H), 7.51-7.64 (m, 3H), 7.72 (m, 3H), 8.07 (m, 2H), 8.12 (s, 1H). MS (DCI-NH_3) m/z 451 $(M+H)^+$, 468 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{19}ClN_2O_3S$: C, 63.92; H, 4.25; N, 6.21. Found: C, 63.69; H, 4.28; N, 6.02.

Example 368

2-(3-Chlorophenyl)-4-cyclohexyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 362 substituting cyclohexylmagnesium chloride in place of cyclopentylmagnesium

chloride (yield: 0.099 g, 68%). M.p. 85-90 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.01-1.30 (m, 3H), 1.48-1.69 (m, 3H), 1.75 (m, 2H), 2.28 (m, 2H), 2.57 (m, 1H), 3.16 (s, 3H), 7.35-7.46 (m, 2H), 7.50-7.62 (m, 3H), 7.68 (m, 2H), 8.11 (m, 2H). MS (DCI-NH_3) m/z 443 $(M+H)^+$, 460 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{23}ClN_2O_3S$ (1.25 H_2O): C, 59.34; H, 5.52; N, 6.01. Found: C, 59.02; H, 5.24; N, 5.65.

Example 369

2-(3-Chlorophenyl)-4-(4-fluorobenzyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228, substituting 4-fluorobenzyl magnesium chloride in place of cyclopentyl magnesium chloride (yield: 0.1895 g, 41%). M.p. 183-185 °C. ^1H NMR (300 MHz, DMSO d_6) δ 3.25-3.36 (3H, obstructed by H_2O), 3.89 (bs, 2H), 6.97-7.09 (m, 4H), 7.50-7.64 (m, 3H), 7.71 (m, 3H), 8.06 (m, 2H), 8.11 (s, 1H). MS (DCI-NH_3) m/z 469 $(M+H)^+$, 486 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{18}ClFN_2O_3S$: C, 61.47; H, 3.87; N, 5.97. Found: C, 61.23; H, 3.84; N, 5.77.

Example 370

2-(3-Chlorophenyl)-4-(4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 362 substituting p-tolylmagnesium bromide in place of cyclopentylmagnesium chloride (yield: 65 mg, 40.9%). M.p. 222-224 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 2.28 (s, 3H), 3.25 (s, 3H), 7.12 (t, 4H), 7.6 (m, 5H), 7.79 (t, 1H) 7.9 (d, J = 9 Hz, 2H), 8.22 (s, 1H). MS (DCI-NH_3) m/z 451 $(M+H)^+$, 468 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{19}ClN_2O_3S \cdot 0.25\ H_2O$: C, 63.92; H, 4.25; N, 6.21. Found: C, 62.99; H, 4.28; N, 5.85.

Example 371

2-(3,4-Difluorophenyl)-4-(3-fluoro-4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(3,4-Difluorophenyl)-4-(3-fluoro-4-methylphenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone was prepared according to the method of Example 362, starting with 2-(3,4-difluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting 3-fluoro-4-methylphenylmagnesium bromide in place of cyclohexylmagnesium chloride to provide the methyl sulfide compound.

The methyl sulfide was oxidized according to the method of Example 10 to provide the title compound (yield: 265 mg, 85.4%). M.p. 204-206 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.25 (br s, 3H), 3.08 (s, 3H), 6.83 (dd, J = 9 Hz, 1.5 Hz, 1H), 6.96 (dd, J = 9 Hz, 1.5 Hz, 1H), 7.08 (t, J = 9 Hz, 1H), 7.23-7.33 (m, 1H), 7.41 (d, J = 9 Hz, 2H), 7.49-7.56 (m, 1H), 7.61-7.69 (m, 1H), 7.93 (d, J = 9 Hz, 2H), 7.99 (s, 1H). MS (DCI-NH_3) m/z 471 $(M+H)^+$, 488 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{17}F_3N_2O_3S$: C, 61.28; H, 3.62; N, 5.96. Found: C, 61.07; H, 3.95; N, 5.56.

Example 372

2-(3-Chlorophenyl)-4-(phenethyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228, starting with 2-(3-chlorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone and substituting phenethyl magnesium chloride in place of cyclohexylmagnesium chloride then oxidizing by the method of Example 10 (yield: 0.100 g, 39%). M.p. 142-145 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 2.80 (m, 4H), 3.30 (s, 3H), 7.01 (m, 2H), 7.21 (m, 3H), 7.51-7.60 (m, 4H), 7.63 (m, 1H), 7.78 (m, 1H), 8.03 (m, 3H). MS (DCI-NH_3) m/z 465 $(M+H)^+$, 482 $(M+NH_4)^+$. Anal. calc. for $C_{25}H_{21}ClN_2O_3S$: C, 64.58; H, 4.55; N, 6.02. Found: C, 64.24; H, 4.50; N, 5.90.

Example 373

2-(3-Chlorophenyl)-4-(2-methylpropoxy)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

373A. 2-(3-Chlorophenyl)-4-(2-methylpropoxy)-5-bromo-3(2H)-pyridazinone.

The title compound is prepared according to the method of Example 194B, starting with 2-(3-chlorophenyl)-4,5-dibromo-3(2H)-pyridazinone (Example 207A) in place of 2-(4-fluorophenyl)-4,5-dibromo-3(2H)-pyridazinone ans substituting 2-methyl-1-propanol in place of methanol.

373B. 2-(3-Chlorophenyl)-4-(2-methylpropoxy)-5-[3-fluoro-4-(methylthio)phenyl]-3(2H)-pyridazinone

The title compound is prepared according to the method of Example 6, starting with 2-(3-chlorophenyl)-4-(2-methylpropoxy)-5-bromo-3(2H)-pyridazinone in place of 2-benzyl-4-bromo-5-methoxy-3(2H)-pyridazinone and substituting 3-fluoro-4-(methylthio)benzeneboronic acid (Example 72C) in place of 4-fluorobenzeneboronic acid.

373C. 2-(3-Chlorophenyl)-4-(2-methylpropoxy)-5-[3-fluoro-4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone

The methyl sulfide compound was oxidized according to the method of Example 10 to provide the title compound (yield: 0.73 g, 100%). M.p. 180-183 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 0.82 (d, J = 6 Hz, 2H), 3.30-3.39 (3H, obstructed by H_2O) 4.25 (d, J = 6 Hz, 2H), 7.57 (m, 3H), 7.75 (m, 1H), 7.85 (m, 1H), 8.00 (m, 1H), 8.23 (s, 1H). MS (DCI-NH_3) m/z 451 $(M+H)^+$, 468 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{20}ClFN_2O_4S$: C, 55.94; H, 4.47; N, 6.21. Found: C, 55.73; H, 4.58; N, 6.01.

Example 374

2-(3-Chlorophenyl)-4-(benzyloxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

To a stirred solution of 2-(3-chlorophenyl)-4-hydroxy-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone (Example 332) (0.100 g, 0.28 mmol) in DMF (2.8 mL) was added benzyl chloride (0.32 mL, 0.28 mmol). The resulting solution was stirred with heating to 60 °C overnight. The solvent was removed *in vacuo* and the resulting residue partitioned between ethyl acetate and 10% citric acid. After extracting with ethyl acetate, the combined organics were dried over $MgSO_4$ and concentrated *in vacuo.* The crude product was purified using flash chromatography (SiO_2, 1:1 ethyl acetate:hexanes) to provide the desired product (yield: 0.096 g, 76%). M.p. 110-113 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 3.39 (s, 3H), 5.48 (s, 2H), 7.29 (m, 4H), 7.59-7.71 (m, 3H), 7.76 (m, 3H), 8.00 (m, 2H), 8.21 (s, 1H). MS (DCI-NH_3) m/z 467 $(M+H)^+$, 484 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{19}ClN_2O_4S$: C, 61.73; H, 4.10; N, 6.00. Found: C, 62.00; H, 4.18; N, 5.93.

Example 375

2-(4-Fluorophenyl)-4-(3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(4-Fluorophenyl)-4-methoxy-5-bromo-3(2H)-pyridazinone (Example 194B) is converted into 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone according to the method of Example 194C followed by the oxidation method in Example 10. The methoxy compound is converted to the 2-(3-chlorophenyl)-4-hydroxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, by treatment with NaOH according to the procedure of Example 332. The hydroxy compound is treated with p-toluenesulfonyl chloride according to the procedure of Example 333, to furnish 2-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-4-tosyloxy-3(2H)-pyridazinone.

The title compound was prepared according to the method of Example 335, starting with 2-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-4-tosyloxy-3(2H)-pyridazinone in place of 2-(3-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-4-tosyloxy-3(2H)-pyridazinone substituting 3-methyl-1-butanol in place of isobutanol (yield: 0.3932 g, 94%). M.p. 117-120 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 0.79 (d, J = 6 Hz, 6H), 1.41-1.59 (m, 3H), 3.30 (s, 3H), 4.42 (d, J = 5 Hz, 2H), 7.36 (m, 2H), 7.65 (m, 2H), 7.90 (m, 2H), 8.06 (m, 2H), 8.18 (s, 1H). MS (DCI-NH_3) m/z 431 $(M+H)^+$, 448 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{23}FN_2O_4S$: C, 61.38; H, 5.39; N, 6.51. Found: C, 61.42; H, 5.30; N, 6.40.

Example 376

2-(4-Fluorophenyl)-4-(2-methylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 2-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-4-tosyloxy-3(2H)-pyridazinone (prepared as an intermediate in Example 375) in place of 2-(3-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-4-tosyloxy-3(2H)-pyridazinone (yield: 0.486 g, 100%). M.p. 121-128 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 0.78 (d, J = 7 Hz, 6H), 1.84 (m, 1H), 3.30 (s, 3H), 4.20 (d, J = 6 Hz, 2H), 7.37 (m, 2H), 7.66 (m, 2H), 7.92 (m, 2H), 8.07 (m, 2H), 8.19 (s, 1H). MS (DCI-NH_3) m/z 417 $(M+H)^+$, 434 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{21}FN_2O_4S \cdot 0.50\ H_2O$: C, 59.28; H, 5.21; N, 6.58. Found: C, 59.49; H, 4.97; N, 6.34.

Example 377

2-(4-Fluorophenyl)-4-(4-fluorobenzyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62, starting with 4-(4-fluorophenylmethyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and reacting with 1-iodo-4-fluorobenzene (yield: 0.0881 g, 78%). M.p. 175-177 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 3.27-3.36 (3H, obstructed by H_2O), 3.88 (bs, 2H), 6.98-7.09 (m, 4H), 7.34 (m, 2H), 7.65 (m, 2H), 7.71 (m, 2H), 8.06 (m, 3H). MS (DCI-NH_3) m/z 453 $(M+H)^+$, 470 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{18}F_2N_2O_3S$: C, 63.71; H, 4.01; N, 6.19. Found: C, 63.61; H, 4.26; N, 6.03.

Example 378

2-(4-Fluorophenyl)-4-(3-methylbutyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228, substituting 3-methylbutyl magnesium bromide in place of cyclohexylmagnesium chloride (yield: 0.325 g, 69%). M.p. 151-154 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 0.75 (d, J = 7 Hz, 6H), 1.32-1.51 (m, 3H), 3.31 (s, 3H), 7.37 (m, 2H), 7.66 (m, 2H), 7.77 (m, 2H), 8.00 (s, 1H), 8.10 (m, 2H). MS (DCI-NH_3) m/z 415 $(M+H)^+$, 432 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{23}FN_2O_3S{\cdot}0.50\ H_2O$: C, 62.39; H, 5.71; N, 6.61. Found: C, 62.04; H, 5.78; N, 6.46.

Example 379

2-(Tetrahydro-2H-pyrano-2-yl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

To the solution of 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone prepared according to Example 11 (172 mg, 0.5 mmol) and p-toluenesulfonic acid hydrate (19 mg, 0.1 mmol) in dioxane (10 mL) was added 2,3-dihydropyran (2 mL). The mixture was stirred at room temperature for 6 hours. The mixture was then poured into a solution of saturated $NaHCO_3$ and extracted with ethyl acetate. The ethyl acetate was concentrated *in vacuo* and the residue was chromatographed (silica gel, 1:1 hexanes-ethyl acetate) to provide the title compound (yield: 25 mg, 11%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.54 (m, 2H), 1.74 (m, 2H), 2.00 (m, 1H), 2.17 (m, 1H), 3.23 (s, 3H), 3.62 (m, 1H), 4.00 (m, 1H), 5.98 (m, 1H), 7.13 (7, J = 9 Hz, 2H), 7.23 (m, 2H), 7.47 (d, J = 9 Hz, 2H), 7.86 (d, J = 9 Hz, 2H), 8.12 (s, 1H). MS (DCI-NH_3) m/z 429 $(M+H)^+$.

Example 380

2-(3-(4-Fluorophenyl)phenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 4, starting with 2-(3-bromophenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 166) in place of 2-benzyl-4-bromo-5-[4-(methylthio)-phenyl]-3(2H)-pyridazinone and substituting cesium fluoride for sodium carbonate (yield: 0.62g, 62%). M.p. 222-225 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 3.24 (s, 3H), 7.16 (m, 2H), 7.36 (m, 3H), 7.53 (m, 2H), 7.64 (m, 2H), 7.73-7.81 (m, 3H), 7.93 (m, 3H), 8.27 (s, 1H). MS (DCI-NH_3) m/z 515 $(M+H)^+$, 532 $(M+NH_4)^+$. Anal. calc.

for $C_{29}H_{20}F_2N_2O_3S \cdot 0.25\ H_2O$: C, 67.10; H, 3.98; N, 5.35. Found: C, 66.93; H, 3.99; N, 5.17.

Example 381

2-(2,2,2-Trifluoroethyl)-4-(2,2-dimethylpropoxy)-5-[3-fluoro-4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

2-(2,2,2-Trifluoroethyl)-4-(2,2-dimethylpropoxy)-5-[3-fluoro-4-(methylthio)-phenyl]-3(2H)-pyridazinone was prepared according to the method of Example 261, substituting 2-(2,2,2-trifluoroethyl)-4-chloro-5-[3-fluoro-4-(methylthio)phenyl]-3(2H)-pyridazinone in place of 2-(2,2,2-trifluoroethyl)-4-chloro-5-[4-(methyl-sulfonyl)phenyl]-3(2H)-pyridazinone.

The methyl sulfide was oxidized with one equivalent of *meta*-chloroperoxy-benzoic acid to give the methyl sulfoxide. The sulfoxide was converted to the title compound according to the method of Example 68 (yield: 196 mg, 28%). M.p. 144-145 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (s, 9H), 4.23 (s, 2H), 4.82 (q, J = 8 Hz, 2H), 5.10 (s, 2H), 7.46 (s, 1H), 7.48 (br s, 1H), 7.79 (s, 1H), 8.03 (t, J = 8 Hz, 1H). MS (DCI-NH_3) m/z 438 $(M+H)^+$. Anal. calc. for $C_{17}H_{19}F_3N_3O_4S$: C, 46.68; H, 4.38; N, 9.61. Found: C, 46.76; H, 4.30; N, 9.52.

Example 382

2-(2,2,2-Trifluoroethyl)-4-(2-methylpropoxy)-5-[3-fluoro-4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 68 substituting 2-(2,2,2-trifluoroethyl)-4-(2-methylpropoxy)-5-[4-(methylsulfinyl)phenyl]-3(2H)-pyridazinone in place of 2-(2,2,2-trifluoroethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfinyl)phenyl]-3(2H)-pyridazinone (yield: 260 mg, 26%). M.p. 163-164 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, J = 6.6 Hz, 6H), 1.91 (septet, J = 6.6 Hz, 1H), 4.34 (d, J = 6.6 Hz, 2H), 5.11 (br s, 2H), 7.43-7.52 (m, 2H), 7.80 (s, 1H), 8.02 (t, J = 8 Hz, 1H). MS (DCI-NH_3) m/z 424 (M+H)+, m/z 441 $(M+NH_4)$+. Anal. calc. for $C_{16}H_{17}F_4N_3O_4S$: C, 45.39; H, 4.05; N, 9.92. Found: C, 59.89; H, 3.83; N, 8.61.

Example 383

2-Benzyl-4-(4-fluorobenzyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 384, substituting 2-benzyl-4-(4-fluorophenylmethyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(3,4-difluorophenyl)-4-(4-fluorophenyl)-5-[4-(methyl-

sulfonyl)phenyl]-3(2H)-pyridazinone (yield: 0.5723 g 34%). M.p. 120-123 °C. ^{1}H NMR (300 MHz, DMSO d6) δ 3.83 (bs, 2H), 5.30 (bs, 2H), 6.95-7.06 (m, 4H), 7.28-7.40 (m, 5H), 7.48 (m, 2H), 7.60 (m, 2H), 7.91 (m, 2H), 7.95 (s, 1H). MS (DCI-NH_3) m/z 450 $(M+H)^+$, 467 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{20}FN_3O_3S$: C, 64.13; H, 4.48; N, 9.35. Found: C, 63.76; H, 4.71; N, 9.02.

Example 384

2-Benzyl-4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

To a solution of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (130 mg, 0.3 mmol) and di-t-butylazodicarboxylate (DBAD) (69 mg, 0.3 mmol) in THF (30 mL) at -78 °C was added dropwise a 1 N solution of lithium 1,1,1,3,3,3-hexamethyldisilazide (0.9 mL, 0.9 mmol) in THF. After addition, the reaction was stirred an additional 45 minutes at -78 °C (or until the TLC indicated a disappearance of starting material). The reaction was quenched with a saturated solution of NH_4Cl and extracted with ethyl acetate. The acetate extract was dried over $MgSO_4$ and concentrated *in vacuo* to obtain 220 mg of crude adduct.

The above adduct was dissolved in THF (30 ML) and was treated at room temperature with 1 N NaOH (3 mL) for 5 hours. Sodium acetate (NaOAc·3 H_2O, 1.38 g, 10 mmol) was added followed by addition of hydroxylamine-O-sulfonic acid (1.13 g, 10 mmol) and H_2O (30 mL). The resulting mixture was stirred at room temperature for 18 hours and then extracted with ethyl acetate. The extract was washed with water, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by chromatography (silica gel, 1:1 hexanes-ethyl acetate) to provide the desired product (yield: 70 mg, 54%). M.p. 185-189 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 5.33 (s, 2H), 7.11 (m, 2H), 7.22 (m, 2H), 7.40 (m, 7H), 7.83 (d, J = 9 Hz, 2H), 8.10 (s, 1H). MS (DCI-NH_3) m/z 436 $(M+H)^+$. Anal. calc. for $C_{23}H_{18}FN_3O_3S \cdot 0.75\ H_2O$: C, 61.65; H, 4.26; N, 9.04. Found: C, 61.67; H, 4.61; N, 8.66.

Example 385

2-(4-Fluorophenyl)-4-(4-fluorophenoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The product from Example 108 was converted to the title sulfonamide according to the method of Example 384, (yield: 65 mg, 28.8%). M.p. 227-229 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.08-7.17 (m, 4H), 7.36 (t, J = 3 Hz, 2H), 7.47 (br s,

2H), 7.61-7.69 (m, 2H), 7.83 (d, J = 9 Hz, 2H), 7.93 (d, J = 9 Hz, 2H), 8.40 (s, 1H). MS (DCI-NH_3) m/z 469 $(M+H)^+$, 486 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{15}F_2N_3O_4S$: C, 58.02; H, 3.30; N, 9.24. Found: C, 57.84; H, 3.34; N, 9.01.

Example 386

2-(3,4-Difluorophenyl)-4-(3-fluoro-4-methylphenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The product from Example 371 was converted to the title sulfonamide according to the method of Example 384 (yield: 45 mg, 28%). M.p. 198-200 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 6.87 (dd, J = 9 Hz, 3 Hz, 1H), 7.13 (dt, J = 9 Hz, 3 Hz, 1H), 7.19 (t, J = 7 Hz, 1H), 7.46 (d, J = 9 Hz, 2H), 7.47 (br s, 2H), 7.52-7.69 (m, 2H), 7.79 (d, J = 9 Hz, 2H), 7.82-7.89 (m, 1H), 8.25 (s, 1H). MS (DCI-NH_3) m/z 472 $(M+H)^+$, 489 $(M+NH_4)^+$.

Example 387

2-(4-Fluorophenyl)-4-(3-fluoro-4-methylphenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The product from Example 250 was converted to the title sulfonamide according to the method of Example 384 (yield: 185 mg, 46%). M.p. 187-188 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 2.22 (br s, 3H), 6.87 (dd, J = 9 Hz, 3 Hz, 1H), 7.16 (q, J = 9 Hz, 2H), 7.38 (t, J = 9 Hz, 2H), 7.46 (br s, 2H), 7.47 (d, J = 9 Hz, 2H), 7.67-7.73 (m, 2H), 7.77 (d, J = 9 Hz, 2H), 8.22 (s, 1H). MS (DCI-NH_3) m/z 454 $(M+H)^+$, 471 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{17}F_2N_3O_3S \cdot 0.25\ H_2O$: C, 60.36; H, 3.87; N, 9.19. Found: C, 60.30; H, 4.26; N, 8.83.

Example 388

2-(3,4-Difluorophenyl)-4-(4-fluorophenoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The product from Example 109 was converted to the title sulfonamide according to the method of Example 384 (yield: 110 mg, 45.7%). M.p. 224-226 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 4.86 (br s, 2H), 6.89-7.03 (m, 4H), 7.19-7.30 (m, 1H), 7.45-7.52 (m, 1H), 7.56-7.66 (m, 1H), 7.79 (d, J = 9 Hz, 2H), 8.04 (d, J = 9 Hz, 1H), 8.08 (s, 1H). MS (DCI-NH_3) m/z 474 $(M+H)^+$, 491 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{14}F_3N_3O_4S \cdot 0.25\ H_2O$: C, 55.32; H, 2.93; N, 8.80. Found: C, 55.26; H, 3.11; N, 8.58.

Example 389

2-(3-Chloro-4-fluorophenyl)-4-(4-fluoro-3-methylphenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The product from Example 247 was converted to the title sulfonamide according to the method of Example 384 (yield: 230 mg, 38%). M.p. 243-245 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.17 (br s, 3H), 6.94-7.09 (m, 2H), 7.25 (dd, J = 9 Hz, 3 Hz, 1H), 7.41-7.48 (m, 4H), 7.60 (t, J = 9 Hz, 1H), 7.68-7.75 (m, 1H), 7.77 (d, J = 9 Hz, 2H), 7.95 (dd, J = 6 Hz, 3 Hz, 1H), 8.25 (s, 1H). MS (DCI-NH_3) m/z 469 $(M+H)^+$, 486 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{16}ClF_2N_3O_3S$: C, 56.67; H, 3.29; N, 8.63. Found: C, 56.81; H, 3.35; N, 8.95.

Example 390

2-(4-Fluorophenyl)-4-(4-fluoro-3-methylphenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The methyl sulfone product of Example 245 was converted to the title sulfonamide according to the method of Example 384 (yield: 78 mg, 28.3%). M.p. 202-204 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.22 (s, 3H), 4.86 (s, 2H), 6.83-6.91 (m, 2H), 7.14-7.25 (m, 3H), 7.36 (d, J = 9 Hz, 2H), 7.65-7.72 (m, 2H), 7.91 (d, J = 9 Hz, 2H), 8.0 (s, 1H). MS (DCI-NH_3) m/z 454 $(M+H)^+$, 471 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{17}F_2N_3O_3S \cdot 0.25\ H_2O$: C, 60.36; H, 3.77; N, 9.19. Found: C, 60.24; H, 3.93; N, 9.25.

Example 391

2-(3-Chlorophenyl)-4-(4-fluoro-3-methylphenyl)-5-[4-(aminosulfonyl)phenyl]-3(2h)-pyridazinone

The methyl sulfone product of Example 244was converted to the title sulfonamide according to the method of Example 384 (yield: 125 mg, 39%). M.p. 187-188 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21 (s, 3H), 4.71 (s, 2H), 6.85-6.92 (m, 2H), 7.21 (d, J = 9 Hz, 1H), 7.32-7.47 (m, 2H), 7.37 (d, J = 9 Hz, 2H), 7.64 (dt, J = 7 Hz, 3 Hz, 1H), 7.77 (br s, 1H), 7.91 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 470 $(M+H)^+$, 487 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{17}ClFN_3O_3S \cdot 0.25\ H_2O$: C, 58.32; H, 3.65; N, 8.88. Found: C, 58.27; H, 3.91; N, 8.62.

Example 392

2-(3-Chlorophenyl)-4-(3-methylbutyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 384, substituting 2-(3-chlorophenyl)-4-(3-methylbutyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 366) in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 0.0756 g, 16%). M.p. 167-170 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 0.78 (d, J = 6 Hz, 6H), 1.47 (5H, obstructed by hexanes), 7.51-7.65 (m, 4H), 7.68 (m, 2H), 7.75 (m, 1H), 7.98 (m, 2H), 8.03 (s, 1H), 8.60 (bs, 1H). MS (DCI-NH_3) m/z 432 $(M+H)^+$, 449 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{22}ClN_3O_3S$ (0.25 $H_2$0): C, 57.79; H, 5.19; N, 9.62. Found: C, 57.78; H, 5.02; N, 9.40.

Example 393

2-(3-Chlorophenyl)-4-(phenethyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 384, substituting 2-(3-chlorophenyl)-4-(phenethyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 372) in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methyl-sulfonyl)phenyl]-3(2H)-pyridazinone (yield: 0.075 g, 17%). semi-solid; ^{1}H NMR (300 MHz, DMSO d_6) δ 2.80 (m, 4H), 3.29-3.42 (3H, obstructed by H_2O), 6.96 (m, 2H), 7.14-7.28 (m, 3H), 7.46-7.68 (m, 7H), 7.78 (m, 1H), 7.92 (m, 2H), 8.01 (s, 1H). MS (DCI-NH_3) m/z 466 $(M+H)^+$, 483 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{20}ClN_2O_3S{\cdot}0.25\ H_2O$: C, 61.27; H, 4.39; N, 8.93. Found: 61.18; H, 4.68; N, 8.58.

Example 394

2-(3-Chlorophenyl)-4-(3-methylbutoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 384, substituting 2-(3-chlorophenyl)-4-(3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 339) in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 0.575 g, 18%). M.p. 137-139 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 0.81 (d, J = 7 Hz, 6H), 1.49 (m, 2H), 1.57 (m, 1H), 4.42 (t, J = 7 Hz, 2H), 7.44-7.65 (m, 5H), 7.76 (m, 1H), 7.84 (m, 2H), 7.94 (m, 2H), 8.20 (s, 1H). MS (DCI-NH_3) m/z 448 $(M+H)^+$, 465 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{22}ClN_3O_4S$: C, 56.31; H, 4.95; N, 9.38. Found C, 56.02; H, 4.82; N, 9.31.

Example 395

2-(3-Chlorophenyl)-4-(2-methylpropoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 384, substituting 2-(3-chlorophenyl)-4-(2-methylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 335) in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 0.0458 g, 25%). M.p. 80-85 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 0.80 (d, J = 6 Hz, 6H), 1.74-1.92 (m, 3H), 4.20 (d, J = 6 Hz, 2H), 7.49-7.64 (m, 5H), 7.76 (m, 1H), 7.85 (m, 2H), 7.95 (m, 2H), 8.21 (m, 1H). MS (DCI-NH_3) m/z 434 $(M+H)^+$, 451 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{20}ClN_3O_4S$: C, 55.36; H, 4.65; N, 9.68. Found: C, 55.12; H, 4.58; N, 9.42.

Example 396

2-(4-Fluorophenyl)-4-(3-methylbutyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 384, substituting 2-(4-fluorophenyl)-4-(3-methylbutyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 378) in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (0.090 g 21%). M.p. 180-183 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 0.78 (d, J = 6 Hz, 6H), 1.49 (m, 5H), 7.36 (m, 2H), 7.53 (m, 2H), 7.62-7.73 (m, 4H), 7.98 (m, 3H). MS (DCI-NH_3) m/z 416 $(M+H)^+$, 433 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{22}FN_3O_3S$: C, 60.71; H, 5.34; N, 10.11. Found: C, 60.37, H, 5.36, N, 9.84.

Example 397

2-(4-Fluorophenyl)-4-(2-methylpropoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 384, substituting 2-(4-fluorophenyl)-4-(2-methylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 376) in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 0.024 g, 6%). M.p. 132-136 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 0.79 (d, J = 6 Hz, 6H), 1.83 (m, 1H), 4.19 (d, J = 6 Hz, 2H), 7.36 (m, 2H), 7.50 (m, 2H), 7.66 (m, 2H), 7.84 (m, 2H), 7.95 (m, 2H), 8.18 (s, 1H). MS (DCI-NH_3) m/z 418 $(M+H)^+$, 435 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{20}FN_3O_4S$: C, 57.54; H, 4.83; N, 10.07. Found C, 57.26; H, 5.00; N, 9.78.

Example 398

2-(4-Fluorophenyl)-4-(3-methylbutoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 384, substituting 2-(4-fluorophenyl)-4-(3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 375) in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 0.051 g, 18%). Yellow oil. ^1H NMR (300 MHz, DMSO d_6) δ 0.80 (d, J = 5 Hz, 6H), 1.47 (m, 3H), 4.42 (t, J = 6 Hz, 2H), 7.37 (m, 2H), 7.50 (m, 1H), 7.65 (m, 2H), 7.83 (m, 2H), 7.93 (m, 2H), 8.18 (s, 1H), 8.60 (bs, 1H). MS (DCI-NH_3) m/z 432 $(M+H)^+$, 449 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{22}FN_3O_4S$: C, 58.46; H, 5.14; N, 9.74. Found: C, 58.16; H, 5.21; N, 9.57.

Example 399

2-(*t*-Butyl)-4-(3-methyl-1-butoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

2-(*t*-Butyl)-4-(3-methyl-1-butoxy)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone prepared in Example 330C was oxidized with one equivalent of *meta*-chloroperoxybenzoic acid to the corresponding methyl sulfoxide. The sulfoxide was converted to the title sulfonamide by the method of Example 68 (yield: 1.25 g, 54%). M.p. 153-155°C. ^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, J = 6 Hz, 2H), 1.48 (q, J = 6 Hz, 2H), 1.49-1.69 (m, 1H), 1.70 (s, 9H), 4.37 (t, J = 6 Hz, 2H), 4.32 (s, 2H), 7.70 (d, J = 9 Hz, 2H), 7.72 (s, 1H), 8.01 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 394 $(M+H)^+$. Anal. calc. for $C_{19}H_{27}N_3O_4S$: C, 57.99; H, 6.91; N, 10.67. Found: C, 58.11; H, 6.71; N, 10.58.

Example 400

2-(3,4-Difluorophenyl)-5-[4-(aminosulfonyl)phenyl]-4-(4-fluorophenyl)-3(2H)-pyridazinone

The title compound was prepared according to Example 384 substituting 2-(3,4-difluorophenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 182) in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 950 mg, 54%). M.p. 177-181 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 7.15 (t, 2H), 7.29 (m, 2H), 7.43 (s, 1H), 7.45 (bs, 2H), 7.59 (m, 2H), 7.76 (d, J = 9 Hz, 2H), 7.85 (m, 1H), 8.27 (s, 1H). MS (DCI-NH_3) m/z 458 $(M+H)^+$, 475 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{14}F_3N_3O_3S$: C, 57.77; H, 3.08; N, 9.19. Found, C, 57.22; H, 3.28; N, 8.99.

Example 401

2-(3-Chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 384, substituting 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 380 mg, 47%). M.p. 208-210 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.15 (t, 2H), 7.27 (m, 2H), 7.43 (s, 1H), 7.45 (bs, 2H) 7.51 (d, J = 9 Hz, 4H), 7.6 (t, 1H), 7.7 (m, 1H), 7.75 (d, J = 9 Hz, 2H), 7.94 (dd, 1H), 8.25 (s, 1H). MS (DCI-NH_3) m/z 474 $(M+H)^+$, 491 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{14}F_2Cl_2N_3O_3S{\cdot}0.5\ H_2O$: C, 55.76; H, 2.98; N, 8.87. Found: C, 56.05; H, 3.42; N, 8.65.

Example 402

2-(3,4-Difluorophenyl)-4-(4-fluoro-3-methylphenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of procedure Example 384, substituting 2-(3,4-difluorophenyl)-4-(4-fluoro-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 105 mg, 27%). M.p. 243-245 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.2 (s, 3H), 7.01 (m, 2H), 7.25 (m, 1H), 7.45 (s, 1H), 7.47 (bs, 2H), 7.6 (m, 2H), 7.77 (d, J = 9 Hz, 2H), 7.85 (m, 1H), 8.26 (s, 2H). MS (DCI-NH_3) m/z 472 $(M+H)^+$, 489 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{17}F_3N_2O_3S{\cdot}0.5\ H_2O$: C, 58.59; H, 3.42; N, 8.91. Found: C, 57; H, 4.23; N, 8.89.

Example 403

2-(3,4-Difluorophenyl)-4-(2-methylpropoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 384, substituting 2-(3,4-difluorophenyl)-4-(2-methylpropoxy)-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 35 mg, 42%). M.p. 169-171 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.78 (d, 6H), 1.84, (m, 1H), 4.2 (d, 2H), 7.54 (m, 3H), 7.6 (m, 1H), 7.82 (m, 3H), 7.91 (d, 2H), 8.21 (s, 1H). MS (DCI-NH_3) m/z 436

$(M+H)^+$, 453 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{19}F_2N_3O_4S \cdot 0.25\ H_2O$: C, 55.17; H, 4.40; N, 9.65. Found: C, 54.19; H, 4.25; N, 9.35

Example 404

2-(3,4-Difluorophenyl)-4-(3-methylbutyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 384, substituting 2-(3,4-difluorophenyl)-4-(3-methylbutyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 58 mg, 52%). M.p. 171-173 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 0.75 (d, 6H), 1.4, (m, 3H), 2.48 (m, 2H), 3.3 (s, 3H), 7.51 (m, 1H), 7.65 (m, 1H), 7.75 (d, J = 9 Hz, 2H), 7.81 (m, 1H) 8.05 (s, 1H), 8.12 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 434 $(M+H)^+$, 451 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{21}F_2N_3O_3S \cdot 0.25\ H_2O$: C, 58.19; H, 4.88; N, 9.69. Found: C, 57.69; H, 5.01; N, 9.18.

Example 405

2-(3-Chloro-4-fluorophenyl)-4-(3-methylbutyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 384, substituting 2-(3-chloro-4-fluorophenyl)-4-(3-methylbutyl)-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 102 mg, 61.8%). M.p. 154-156 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 0.75 (d, 6H), 1.4, (m, 3H), 2.48 (m, 2H), 7.54 (s, 2H), 7.6 (m, 1H), 7.69 (m, 2H), 7.93 (dd, 1H), 8.05 (m, 2H). MS (DCI-NH_3) m/z 450 $(M+H)^+$, 468 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{22}FN_2O_3SCl \cdot 0.25\ H_2O$: C, 58.86; H, 4.94; N, 6.24. Found: C, 59.23; H, 5.12; N, 6.00.

Example 406

2-(3,4-Difluorophenyl)-4-(2,2-dimethylpropoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 384 substituting 2-(3,4-difluorophenyl)-4-(2,2-dimethylpropoxy)-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 310 mg, 38%). M.p. 173-175 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 0.8 (s, 9H), 3.3 (s, 3H), 4.1 (s, 2H), 7.51 (m,

3H), 7.6 (m, 1H), 7.85 (m, 3H), 7.95 (d, J = 9 Hz, 2H), 8.21 (s, 1H). MS (DCI-NH_3) m/z 450 $(M+H)^+$, 467 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{21}F_2N_3O_4S$: C, 56.12; H, 4.71; N, 9.35. Found, C, 55.83; H, 4.73; N, 9.08.

Example 407

2-(3,4-Difluorophenyl)-4-(4-fluorophenoxy)-5-[3-fluoro-4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 400 substituting 2-(3,4-difluorophenyl)-4-(4-fluorophenoxy)-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone in place of 2-benzyl-4-(4-fluorophenyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 125 mg, 31%). M.p. 224-226 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 7.15 (d, 4H), 7.51 (m, 1H), 7.6 (m, 2H) 7.75 (m, 4H), 7.9 (t, 1H); 8.4 (s, 1H). MS (DCI-NH_3) m/z 492 $(M+H)^+$, 509 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{13}F_4N_3O_4S$: C, 53.77; H, 2.67; N, 8.55. Found,; C, 53.33; H, 2.84; N, 8.22

Example 408

2-(3,3-Difluoro-2-propenyl)]-4-(4-fluorophenyl)-5-[3-fluoro-4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The intermediate, 2-benzyl-4-(4-fluorophenyl)-5-[3-fluoro-4-(methylthio)-phenyl]-3(2H)-pyridazinone prepared according to the method of Example 72, was oxidized with one equivalent of *meta*-chloroperoxybenzoic acid to provide the methyl sulfoxide which was converted to the sulfonamide according to the method of Example 68. The sulfonamide material was N-debenzylated according to the method of Example 11 and N-alkylated according to the method of Example 127, substituting 1,3-dibromo-1,1-difluoropropane in place of 3,4-difluorobenzyl bromide and employing 4 equivalents of potassium carbonate to provide the title compound (yield: 120 mg, 27%). M.p. 180-183 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 4.71 (dt, J = 15 Hz, 7.5 Hz, 2H), 4.75 (d, J = 7.5 Hz, 2H), 5.06 (s, 2H), 7.02 (m, 2H), 7.19 (dd, J = 9 Hz, 6 Hz, 2H), 7.81 (s, 1H), 7.87 (t, J = 7.5 Hz, 2H). MS (DCI-NH_3) m/z 440 $(M+H)^+$. Anal. calc. for $C_{19}H_{13}F_4N_3O_3S$: C, 51.93; H, 2.98; N, 9.56. Found: C, 51.71; H, 3.15; N, 9.28.

Example 409

2-(3,4-Difluorophenyl)-4-[2-(2-propoxy)ethoxy]-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 384, substituting 2-(3,4-difluorophenyl)-4-[2-(2-propoxy)ethoxy]-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methyl-sulfonyl)phenyl]-3(2H)-pyridazinone (yield: 110 mg, 34%). M.p. 54-56 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.0 (d, 6H), 3.43 (m, 1H), 3.54 (m, 2H), 4.63 (m, 2H), 7.5 (m, 3H), 7.6 (m, 1H), 7.8 (m, 1H), 7.95 (m, 4H), 8.2 (s, 1H). MS (DCI-NH_3) m/z 466 $(M+H)^+$, 483 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{21}F_2N_3O_5S$: C, 54.19; H, 4.55; N, 9.03. Found, C, 54.29; H, 4.67; N, 8.95.

Example 410

2-(3,4-Difluorophenyl)-4-(4-methyl-3-pentenyloxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 384 substituting 2-(3,4-difluorophenyl)-4-(4-methyl-3-pentenyloxy)-5-[4-(methyl-sulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone. M.p. 70-73 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.5 (d, 6H), 2.27 (m, 2H) 4.43 (t, 2H), 4.5 (m, 1H), 7.5 (m, 2H), 7.6 (m, 1H), 7.8 (m, 2H), 7.92 (d, J = 2 H, 2H), 8.2 (s, 1H). MS (DCI-NH_3) m/z 462 $(M+H)^+$, 479 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{21}F_2N_3O_4S$: C, 57.26; H, 4.59; N, 9.11. Found, : C, 56.96; H, 4.70; N, 9.01.

Example 411

2-(3-Chlorophenyl)-4-(3-fluorophenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 3-fluorophenol in place of isobutanol (yield: 0.034 g, 22%). M.p. 178-180 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 3.27 (s, 3H), 6.88-7.00 (m, 2H), 7.10 (m, 1H), 7.36 (m, 1H), 7.59 (m, 3H), 7.74 (m, 1H), 7.90 (m, 2H), 8.06 (m, 2H), 8.43 (s, 1H). MS (DCI-NH_3) m/z 488 $(M+H)^+$. Anal. calc. for $C_{23}H_{16}ClFN_2O_4S \cdot 0.25\ H_2O$: C, 58.10; H, 3.49; N, 5.89. Found C, 58.04; H, 3.59; N, 5.80.

Example 412

2-(3-Chlorophenyl)-4-(2-methylpropoxy)-5-[3-fluoro-4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 384 , substituting 2-(3-chlorophenyl)-4-(2-methylpropoxy)-5-[3-fluoro-4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methyl-sulfonyl)phenyl]-3(2H)-pyridazinone (yield: 0.019 g, 10%). M.p. 157-159 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 0.81 (d, J = 6 Hz, 6H), 1.86 (m, 1H), 4.24 (d, J = 6 Hz, 2H), 7.75 (m, 3H), 7.66 (m, 1H), 7.73 (m, 2H), 7.83 (m, 2H), 7.91 (m, 1H), 8.23 (s, 1H). Anal. calc. for $C_{21}H_{19}ClFN_3O_4S$: C, 53.16; H, 4.24; N, 9.30. Found: C, 53.02; H, 4.43; N, 9.10.

Example 413

2-(3-Chlorophenyl)-4-(4-methylpentyloxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 4-methyl-1-pentanol in place of isobutanol (yield: 0.137 g, 90%). M.p. 139-140 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 0.74 (d, J = 6 Hz, 6H), 1.03 (m, 2H), 1.39 (m, 1H), 1.54 (m, 2H), 3.29 (s, 3H), 4.40 (t, J = 5 Hz, 2H), 7.51-7.60 (m, 3H), 7.75 (m, 1H), 7.90 (m, 2H), 8.07 (m, 2H), 8.20 (s, 1H). MS (DCI-NH_3) m/z 461 $(M+H)^+$, 478 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{25}ClN_2O_4S$: C, 59.95; H, 5.97; N, 6.08. Found: C, 59.62; H, 5.63; N, 5.86.

Example 414

2-(4-Fluorophenyl)-4-(4-methylpentyloxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, starting with 2-(4-fluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(3-chlorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone and substituting 4-methyl-1-pentanol in place of isobutanol (yield: 0.128 g, 85%). M.p. 123-125 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 0.74 (d, J = 6 Hz, 6H), 1.03 (m, 2H), 1.39 (m, 1H), 1.54 (m, 2H), 3.28 (s, 3H), 4.39 (t, J = 6 Hz, 2H), 7.37 (m, 2H), 7.66 (m, 2H), 7.91 (m, 2H), 8.07 (m, 2H), 8.18 (s, 1H).

MS (DCI-NH_3) m/z 445 $(M+H)^+$. Anal. calc. for $C_{23}H_{25}FN_2O_4S$: C, 62.14; H, 5.67; N, 6.30. Found: C, 62.28; H, 5.59; N, 6.25.

Example 415

2-(4-Fluorophenyl)-4-hydroxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 332, substituting 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone for 2-(3-chlorophenyl)-4-methoxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 2.022 g, 97%). ^{1}H NMR (300 MHz, DMSO d_6) δ 3.28 (s, 3H), 7.38 (m, 2H), 7.70 (m, 2H), 8.03 (m, 4H), 8.22 (s, 1H). MS (APCI-+Q1MS) 361 $(M+H)^+$, (-Q1MS) 359 $(M-H)^-$.

Example 416

2-(4-Fluorophenyl)-4-cyclopropylmethoxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 2-(4-fluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(3-chlorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone and substituting cyclopropylmethanol in place of isobutanol (yield: 0.117 g, 83%). M.p. 166-167 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 0.22 (m, 2H), 0.46 (m, 2H), 1.10 (m, 1H), 3.31 (s, 3H), 4.30 (d, J = 7 Hz, 2H), 7.36 (m, 2H), 7.66 (m, 2H), 7.96 (m, 2H), 8.07 (m, 2H), 8.20 (s, 1H). MS (DCI-NH_3) m/z 415 $(M+H)^+$, 432 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{25}ClN_2O_4S$: C, 60.86; H, 4.62; N, 6.76. Found: C, 60.76; H, 4.72; N, 6.61.

Example 417

2-(4-Fluorophenyl)-4-(2-cyclopropyl-1-ethoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 2-(4-fluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-

pyridazinone in place of 2-(3-chlorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone and substituting 2-cyclopropane ethanol in place of isobutanol (yield: 0.1472 g, 100%). M.p. 111-117 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ -0.01 (m, 2H), 0.31 (m, 2H), 0.60 (m, 1H), 1.49 (q, J = 6 Hz, 2H), 3.29 (s, 3H), 4.48 (t, J = 6 Hz, 2H), 7.37 (m, 2H), 7.65 (m, 2H), 7.91 (m, 2H), 8.06 (m, 2H), 8.17 (s, 1H). MS (DCI-NH_3) m/z 429 $(M+H)^+$, 446 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{21}FN_2O_4S$: C, 61.67; H, 4.94; N, 6.54. Found: C, 61.59; H, 5.02; N, 6.45.

Example 418

2-(3-Chlorophenyl)-4-cyclopropanemethoxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting cyclopropane methanol in place of isobutanol (yield: 0.0917 g, 64%). M.p. 158-161 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 0.22 (m, 2H), 0.46 (m, 2H), 1.13 (m, 1H), 3.31 (s, 3H), 4.31 (d, J = 7 Hz, 2H), 7.57 (m, 3H), 7.75 (m, 1H), 7.96 (m, 2H), 8.08 (m, 2H), 8.23 (s, 1H). MS (DCI-NH_3) m/z 431 $(M+H)^+$, 448 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{19}ClN_2O_4S \cdot 0.25\ H_2O$: C, 57.92; H, 4.51; N, 6.43. Found: C, 57.86; H, 4.35; N, 6.27.

Example 419

2-(3-Chlorophenyl)-4-(2-cyclopropane-1-ethoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 2-cyclopropane ethanol in place of isobutanol (yield: 0.114 g, 78%). M.p. 124-128 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 0.00 (m, 2H), 0.32 (m, 2H), 0.61 (m, 1H), 1.49 (q, J = 6 Hz, 2H), 3.30 (s, 3H), 4.50 (t, J = 6 Hz, 2H), 7.58 (m, 3H), 7.76 (m, 1H), 7.91 (m, 2H), 8.07 (m, 2H), 8.21 (s, 1H). MS (DCI-NH_3) m/z 445 $(M+H)^+$, 462 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{21}ClN_2O_4S$: C, 59.39; H, 4.76; N, 6.30. Found: C, 58.92; H, 4.94; N, 6.15.

Example 420

2-(4-Fluorophenyl)-4-(4-methylpentyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 362, substituting 2-(4-fluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(3-chlorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone and substituting 4-methylpentane-1-magnesium bromide for cyclopropyl magnesium chloride (yield: 0.165 g, 99%). M.p. 112-115 °C. ^1H NMR (300 MHz, DMSO d_6) δ 0.75 (d, J = 7 Hz, 6H), 1.07 (q, J = 7 Hz, 2H), 1.32-1.53 (m, 3H), 2.45 (t, 2H), 3.31 (s, 3H), 7.37 (m, 2H), 7.66 (m, 2H), 7.76 (m, 2H), 8.00 (s, 1H), 8.10 (m, 2H). MS (DCI-NH_3) m/z 429 $(M+H)^+$. 446 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{25}FN_2O_3S$: C, 64.47; H, 5.88; N, 6.54. Found: C, 64.44; H, 5.90; N, 6.49.

Example 421

2-(3-Chlorophenyl)-4-(4-methylpentyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 362, substituting 4-methylpentane-1-magnesium bromide in place of cyclopropyl magnesium chloride (yield: 165 mg, 98%). oil. ^1H NMR (300 MHz, DMSO d_6) δ 0.76 (d, J = 6 Hz, 6H), 1.07 (m, 2H), 1.33-1.55 (m, 3H), 2.45 (m, 2H), 3.32 (s, 3H), 7.51-7.65 (m, 4H), 7.76 (m, 2H), 8.03 (s, 1H), 8.11 (m, 2H). MS (DCI-NH_3) m/z 445 $(M+H)^+$, 462 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{25}ClN_2O_3S$: C, 62.06; H, 5.66; N, 6.30. Found: C, 61.86; H, 5.64; N, 6.18.

Example 422

2-(4-Fluorophenyl)-4-(3-methyl-2-butenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 2-(4-fluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(3-chlorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone and substituting 3-methyl-2-buten-1-ol in place of isobutanol (yield: 0.1284 g, 88%). M.p. 128-132 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 1.58 (s, 3H), 1.67 (s, 3H), 3.30 (s, 3H), 4.95 (d, J = 7 Hz, 2H), 5.31 (m, 1H), 7.38 (m, 2H), 7.65 (m, 2H), 7.89 (m, 2H), 8.06 (m, 2H), 8.18 (s, 1H). MS (DCI-NH_3) m/z 429 $(M+H)^+$, 446 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{21}FN_2O_4S$: C, 61.67; H, 4.94; N, 6.54. Found: C, 61.41; H, 4.95; N, 6.47.

Example 423

2-(3-Chlorophenyl)-4-(3-methyl-2-butenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 3-methyl-2-buten-1-ol in place of isobutanol (yield: 0.119 g, 81%). M.p. 113-115 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 1.58 (s, 3H), 1.67 (s, 3H), 3.31 (s, 3H), 4.96 (m, 2H), 5.32 (m, 1H), 7.58 (m, 3H), 7.75 (m, 1H), 7.89 (m, 2H), 8.07 (m, 2H), 8.21 (s, 1H). MS (APCI+Q1MS) 445 $(M+H)^+$, (APCI-Q1MS) 479 $(M+35)^-$. Anal. calc. for $C_{22}H_{21}ClN_2O_4S$: C, 59.39; H, 4.76; N, 6.30. Found: C, 59.14; H, 4.66; N, 6.16.

Example 424

2-(4-Fluorophenyl)-4-(4-methyl-3-pentenyloxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 2-(4-fluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(3-chlorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)-

phenyl]-3(2H)-pyridazinone and substituting 4-methyl-2-penten-1-ol in place of isobutanol (yield: 0.1165 g, 77%). M.p. 111-114 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 1.46 (s, 3H), 1.56 (s, 3H), 2.26 (m, 2H), 3.30 (s, 1H), 4.43 (t, J = 7 Hz, 2H), 4.96 (m, 1H), 7.37 (m, 2H), 7.65 (m, 2H), 7.91 (m, 2H), 8.06 (m, 2H), 8.18 (s, 1H). MS (DCI-NH_3) m/z 443 $(M+H)^+$, 460 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{23}FN_2O_4S$: C, 62.43; H, 5.24; N, 6.33. Found: C, 62.32; H, 5.30; N, 6.25.

Example 425

2-(4-Fluorophenyl)-4-(3-methyl-3-butenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 2-(4-fluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(3-chlorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting 3-methyl-3-butene-1-ol in place of isobutanol (yield: 0.1327 g, 91%). M.p. 109-111 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 1.61 (s, 3H), 2.32 (t, J = 7 Hz, 2H), 3.30 (s, 3H), 4.56 (t, J = 7 Hz, 2H), 4.63 (bs, 1H), 4.68 (bs, 1H), 7.37 (m, 2H), 7.66 (m, 2H), 7.90 (m, 2H), 8.05 (m, 2H), 8.19 (s, 1H). MS (DCI-NH_3) m/z 429 $(M+H)^+$, 446 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{21}FN_2O_4S$: C, 61.67; H, 4.94; N, 6.54. Found: C, 61.50; H, 5.00; N, 6.45.

Example 426

2-(3-Chlorophenyl)-4-(4-methyl-3-pentenyloxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 4-methyl-3-pentene-1-ol in place of isobutanol (yield: 0.1149 g, 76%). M.p. 110-111 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 1.47 (s, 3H), 1.55 (s, 3H), 2.27 (m, 2H), 3.30 (s, 3H), 4.44 (t, J = 6 Hz, 2H), 4.96 (m, 1H), 7.52-7.64 (m, 3H), 7.75 (m, 1H), 7.91 (M, 2H), 8.06 (m, 2H), 8.21 (s, 1H). MS (DCI-NH_3) m/z 459 $(M+H)^+$, 476 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{23}ClN_2O_4S$: C, 60.19; H, 5.05; N, 6.10. Found: C, 60.06; H, 4.90; N, 5.96.

Example 427

2-(3-Chlorophenyl)-4-(3-methyl-3-butenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 3-methyl-3-butene-1-ol in place of isobutanol (yield: 0.1159 g, 79%). M.p. 110-112 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 1.62 (s, 3H), 2.32 (t, J = 7 Hz, 2H), 3.30 (s, 3H), 4.57 (t, J = 6 Hz, 2H), 4.63 (bs, 1H), 4.68 (bs, 1H), 7.51-7.64 (m, 3H), 7.76 (m, 1H), 7.90 (m, 2H), 8.05 (m, 2H), 8.21 (s, 1H). MS (DCI-NH_3) m/z 445 $(M+H)^+$, 462 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{21}ClN_2O_4S$: C, 59.39; H, 4.76; N, 6.30. Found: C, 59.27; H, 4.68; N, 6.18.

Example 428

2-(4-Fluorophenyl)-4-(1,5-hexadienyl-3-oxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 178, substituting 1,5-hexadien-3-ol in place of 2-ethyl-1-hexanol (yield: 150 mg, 85%). M.p. 104-105 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.42 (m, 2H), 3.30 (s, 3H), 5.00 (m, 2H), 5.17 (m, 2H), 5,64 (m, 2H), 7.36 (t, J = 9 Hz, 2H), 7.64 (m, 2H), 7.92 (d, J = 9 Hz, 2H), 8.06 (d, J = 9 Hz, 2H), 8.19 (s, 1H). MS (APCI+) m/z 441 $(M+H)^+$; (APCI-) m/z 475 $(M+Cl)^-$. Anal. calc. for $C_{23}H_{21}FN_2O_4S$: C, 62.71; H, 4.80; N, 6.35. Found: C, 62.96; H, 4.93; N, 5.85.

Example 429

2-(4-Fluorophenyl)-4-(5-methyl-2-hexyloxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 178, substituting 5-methyl-2-hexanol in place of 2-ethyl-1-hexanol (yield: 150 mg, 82%). M.p. 102-103 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.73 (d, J = 7 Hz, 6H), 1.04 (m,

2H), 1.14 (d, J = 7 Hz, 3H), 1.40 (m, 3H), 3.29 (s, 3H), 5.12 (m, 1H), 7.36 (t, J = 9 Hz, 2H), 7.66 (m, 2H), 7.92 (d, J = 9 Hz, 2H), 8.07 (d, J = 9 Hz, 2H), 8.19 (s, 1H). MS (APCI+) m/z 459 $(M+H)^+$; (APCI-) m/z 493 $(M+Cl)^-$. Anal. calc. for $C_{24}H_{27}FN_2O_4S$: C, 62.86; H, 5.93; N, 6.10. Found: C, 62.83; H, 5.99; N, 6.07.

Example 430

2-(4-Fluorophenyl)-4-(2-ethyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 178, substituting 2-ethyl-1-butanol in place of 2-ethyl-1-hexanol (yield: 140 mg, 80%). M.p. 107-108 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.73 (t, J = 7 Hz, 6H), 1.20 (quintet, J = 7 Hz, 4H), 1.40 (m, 1H), 3.29 (s, 3H), 4.29 (d, J = 7 Hz, 2H), 7.37 (t, J = 9 Hz, 2H), 7.66 (m, 2H), 7.90 (d, J = 9 Hz, 2H), 8.07 (d, J = 9 Hz, 2H), 8.19 (s, 1H). MS (APCI+) m/z 445 $(M+H)^+$; (APCI-) m/z 479 $(M+Cl)^-$. Anal. calc. for $C_{23}H_{25}FN_2O_4S$: C, 62.14; H, 5.66; N, 6.30. Found: C, 62.05; H, 5.86; N, 6.30.

Example 432

2-(4-Fluorophenyl)-4-(2-thioisopropyl-1-ethoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 178, substituting 2-(isopropylthio)ethanol in place of 2-ethyl-1-hexanol (yield: 138 mg, 74%). M.p. 137-139 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.13 (d, J = 7 Hz, 6H), 2.77 (t, J = 7 Hz, 2H), 2.88 (quintet, J = 7 Hz, 1H), 3.29 (s, 3H), 4.58 (t, J = 7 Hz, 2H), 7.37 (t, J = 9 Hz, 2H), 7.66 (m, 2H), 7.92 (d, J = 9 Hz, 2H), 8.06 (d, J = 9 Hz, 2H), 8.18 (s, 1H). MS (APCI+) m/z 463 $(M+H)^+$. Anal. calc. for $C_{22}H_{23}FN_2O_4S_2$: C, 57.12; H, 5.01; N, 6.05. Found: C, 56.82; H, 4.91; N, 5.99.

Example 433

2-(4-Fluorophenyl)-4-(3-methylthio-1-hexyloxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 178, substituting 3-(methylthio)-1-hexanol in place of 2-ethyl-1-hexanol (yield: 155 mg, 79%). M.p. 90-92 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 0.78 (t, J = 7 Hz, 3H), 1.30 (m, 4H), 1.76 (m, 2H), 2.82 (s, 3H), 2.38 (m, 1H), 3.29 (s, 3H), 4.55 (m, 2H), 7.37 (t, J = 9 Hz, 2H), 7.66 (m, 2H), 7.92 (d, J = 9 Hz, 2H), 8.06 (d, J = 9 Hz, 2H), 8.18 (s, 1H). MS (APCI+) m/z 491 $(M+H)^+$; (APCI-) m/z 525 $(M+Cl)^-$. Anal. calc. for $C_{24}H_{27}FN_2O_4S_2$: C, 58.75; H, 5.54; N, 5.70. Found: C, 58.66; H, 5.54; N, 5.66.

Example 434

2-(4-Fluorophenyl)-4-(2-methyl-4-pentenyl-1-oxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 178, substituting 2-methyl-4-penten-1-ol in place of 2-ethyl-1-hexanol (yield: 135 mg, 76%). M.p. 106-107 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 0.76 (d, J = 7 Hz, 3H), 1.78 (m, 2H), 2.00 (m, 1H), 3.29 (s, 3H), 4.25 (m, 2H), 4.90 (m, 2H), 5.67 (m, 1H), 7.37 (t, J = 9 Hz, 2H), 7.66 (m, 2H), 7.92 (d, J = 9 Hz, 2H), 8.06 (d, J = 9 Hz, 2H), 8.18 (s, 1H). MS (APCI+) m/z 443 $(M+H)^+$; (APCI-) m/z 477 $(M+Cl)^-$. Anal. calc. for $C_{23}H_{23}FN_2O_4S$: C, 62.42; H, 5.23; N, 6.33. Found: C, 62.13; H, 5.12; N, 6.22.

Example 435

2-(3,4-Difluorophenyl)-4-(3-trifluoromethyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

To a solution of 2-(3,4-difluorophenyl)-4-hydroxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyidazinone (189mg, 0.5 mmol), Ph_3P (262 mg, 1 mmol) and 3-trifluoromethyl-1-butanol (66 mg, 0.5 mmol) in THF (25 mL) was added dropwise a solution of DIAD (0.2 mL, 1 mmol) in THF (5 mL) and the resulting mixture was stirred at room temperature for 8 hours. The mixture was

concentrated *in vacuo* and the residue was chromatographed (silica gel, 1:1 hexanes-ethyl acetate) to provide the desired product, (yield: 180 mg 71%). M.p. 126-128 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.96 (d, J = 7 Hz, 3H), 1.55 (m, 1H), 1.97 (m, 1H), 2.30 (m, 1H), 3.29 (s, 3H), 4.46 (m, 2H), 7.52 (m, 1H), 7.62 (m, 1H), 7.81 (m, 1H), 7.90 (d, J = 9 Hz, 2H), 8.08 (d, J = 9 Hz, 2H), 8.22 (s, 1H). MS (APCI+) m/z 503 $(M+H)^+$; (APCI-) m/z 537 $(M+Cl)^-$. Anal. calc. for $C_{22}H_{19}F_5N_2O_4S$: C, 52.59; H, 3.81; N, 5.57. Found: C, 52.70; H, 3.73; N, 5.63.

Example 436

2-(3,4-Difluorophenyl)-4-ethoxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 178, starting with 2-(3,4-difluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting ethanol in place of 2-ethyl-1-hexanol (yield: 25 mg, 12%). M.p. 121-123 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.23 (t, J = 7 Hz, 3H), 3.30 (s, 3H), 4.51 (q, J = 7 Hz, 2H), 7.52 (m, 1H), 7.62 (m, 1H), 7.81 (m, 1H), 7.90 (d, J = 9 Hz, 2H), 8.08 (d, J = 9 Hz, 2H), 8.22 (s, 1H). MS (APCI+) m/z 407 $(M+H)^+$; (APCI-) m/z 441 $(M+Cl)^-$. Anal. calc. for $C_{19}H_{16}F_2N_2O_4S{\cdot}0.25\ H_2O$: C, 55.53; H, 4.04; N, 6.81. Found: C, 55.58; H, 4.21; N, 6.61.

Example 437

2-(3,4-Difluorophenyl)-4-(4-methyl-1-pentyloxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 178, starting with 2-(3,4-difluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting 4-methyl-1-pentanol in place of 2-ethyl-1-hexanol (yield: 120 mg, 52%). M.p. 98-99 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.73 (d, J = 7 Hz, 6H), 1.02 (m, 2H), 1.29 (m, 1H), 1.54 (m, 2H), 3.30 (s, 3H), 4.40 (t, J = 7 Hz, 2H), 7.52 (m, 1H), 7.62 (m, 1H), 7.81 (m, 1H), 7.90 (d, J = 9 Hz, 2H), 8.08 (d, J = 9 Hz, 2H), 8.22 (s, 1H). MS (APCI+) m/z 463 $(M+H)^+$; (APCI-) m/z 497

$(M+Cl)^-$. Anal. calc. for $C_{23}H_{24}F_2N_2O_4S$: C, 59.72; H, 5.23; N, 6.05. Found: C, 59.57; H, 5.28; N, 6.01.

Example 438 2-(3,4-Difluorophenyl)-4-(4-methyl-2-pentyloxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 178, starting with 2-(3,4-difluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting 4-methyl-2-pentanol for 2-ethyl-1-hexanol (yield: 115 mg, 50%). M.p. 132-133 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 0.80 (d, J = 7 Hz, 3H), 0.87 (d, J = 7 Hz, 3H), 1.10 (d, J = 7 Hz, 3H), 1.26 (m, 1H), 1.50 (m, 1H), 1.63 (m, 1H), 3.30 (s, 3H), 5.31 (m, 1H), 7.52 (m, 1H), 7.62 (m, 1H), 7.81 (m, 1H), 7.90 (d, J = 9 Hz, 2H), 8.08 (d, J = 9 Hz, 2H), 8.22 (s, 1H). MS (APCI+) m/z 463 $(M+H)^+$; (APCI-) m/z 497 $(M+Cl)^-$. Anal. calc. for $C_{23}H_{24}F_2N_2O_4S$: C, 59.72; H, 5.23; N, 6.05. Found: C, 59.44; H, 5.26; N, 5.99.

Example 439 2-(3,4-Difluorophenyl)-4-(2-cyclopentyl-1-ethoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 178, starting with 2-(3,4-difluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting 2-cyclopentyl-1-ethanol in place of 2-ethyl-1-hexanol (yield: 115 mg, 60%). M.p. 100-101 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 1.00 (m, 2H), 1.38 (m, 2H), 1.57 (m, 7H), 3.30 (s, 3H), 4.42 (t, J = 7 Hz, 2H), 7.52 (m, 1H), 7.62 (m, 1H), 7.81 (m, 1H), 7.90 (d, J = 9 Hz, 2H), 8.08 (d, J = 9 Hz, 2H), 8.22 (s, 1H). MS (APCI+) m/z 475 $(M+H)^+$; (APCI-) m/z 509 $(M+Cl)^-$. Anal. calc. for $C_{24}H_{24}F_2N_2O_4S{\cdot}0.25\ H_2O$: C, 60.17; H, 5.15; N, 5.84. Found: C, 60.12; H, 5.14; N, 5.76.

Example 440

2-(3,4-Difluorophenyl)-4-(2-cyclopent-2-enyl-1-ethoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 178, starting with 2-(3,4-difluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting 2-cyclopent-2-enyl-1-ethanol in place of 2-ethyl-1-hexanol (yield: 95 mg, 48%). M.p. 126-127 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.30 (m, 1H), 1.57 (sextet, J = 7 Hz, 1H), 1.69 (sextet, J = 7 Hz, 1H), 1.87 (m, 2H), 2.57 (m, 1H), 3.30 (s, 3H), 4.45 (m, 2H), 5.60 (m, 1H), 5.68 (m, 1H), 7.52 (m, 1H), 7.62 (m, 1H), 7.81 (m, 1H), 7.90 (d, J = 9 Hz, 2H), 8.08 (d, J = 9 Hz, 2H), 8.22 (s, 1H). MS (APCI+) m/z 473 $(M+H)^+$; (APCI-) m/z 507 $(M+Cl)^-$. Anal. calc. for $C_{24}H_{22}F_2N_2O_4S$: C, 61.00; H, 4.69; N, 5.92. Found: C, 60.76; H, 4.65; N, 5.80.

Example 441

2-(2-Hydroxy-2-phenylethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A mixture of the product from Example 46, 2-phenacyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (700 mg, 1.5 mmol), and sodium borohydride (69 mg, 1.8 mmol) in ethanol (200 mL), was stirred at 40 °C for 2 hours. The reaction mixture was then concentrated *in vacuo* and the residue was partitioned between ethyl acetate and 2 N aqueous hydrochloric acid. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo* to provide a pale yellow solid which was crystallized from ethyl acetate/hexanes to provide the title compound as white crystals (yield: 540 mg, 78%). M.p. 205-207 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.07 (s, 3H), 3.75 (br s, 1H), 4.63-4.47 (m, 2H), 5.33 (dd, J = 9 Hz, 3 Hz, 1H), 7.00 (t, J = 9 Hz, 2H), 7.20 (dd, J = 9 Hz, 3 Hz, 2H), 7.30-7.45 (m, 5H), 7.52 (d, J = 9 Hz, 2H), 7.91 (s, 1H), 7.91 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 465 $(M+H)^+$. Anal. calc. for $C_{25}H_{21}FN_2O_4S$: C, 64.64; H, 4.55; N, 6.03. Found: C, 64.34; H, 4.66; N, 5.93.

Example 442

2-(2-Methoxy-2-phenylethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A mixture of the product from Example 441, 2-(2-hydroxy-2-phenylethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (210 mg, 0.45 mmol), iodomethane (56 µL, 0.90 mmol), and an 80% oil dispersion of sodium hydride (18 mg, 0.59 mmol) in anhydrous DMF (16 mL) was stirred at room temperature for 18 hours. The reaction mixture was partitioned between ethyl acetate and 2 N aqueous hydrochloric acid. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo* to provide a yellow oil which was purified by column chromatography (silica gel, 70:30 hexanes/ethyl acetate). Fractions containing product were combined and concentrated *in vacuo* , and the residue was triturated with hexanes to provide the title compound (yield: 75 mg, 34.7%). M.p. 135-137 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.07 (s, 3H), 3.26 (s, 3H), 4.33-4.52 (m, 2H), 4.91 (dd, J = 9 Hz, 3 Hz, 1H), 6.99 (t, J = 9 Hz, 2H), 7.20 (dd, J = 9 Hz, 3 Hz, 2H), 7.31-7.50 (m, 7H), 7.87 (s, 1H), 7.89 (d, J = 9 Hz, 2H). MS ($DCI-NH_3$) m/z 479 $(M+H)^+$. Anal. calc. for $C_{26}H_{23}FN_2O_4S$: C, 65.25; H, 4.84; N, 5.85. Found: C, 64.98; H, 4.83; N, 5.81.

Example 443

2-(2-Methoxyimino-2-phenylethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A mixture of the product from Example 46, 2-phenacyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (220 mg, 0.476 mmol), methoxylamine hydrochloride (318 mg, 3.8 mmol), and sodium acetate (518 mg, 3.8 mmol) in methanol (100 mL) was stirred at reflux for 48 hours. The reaction mixture was concentrated *in vacuo* , and the residue was partitioned between ethyl acetate and saturated aqueous ammonium chloride. The organic layer was washed with brine then dried over $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo* to provide a brown oil which was purified by column chromatography (silica gel, 70:30 hexanes/ethyl acetate). Fractions containing product were combined and concentrated *in vacuo* . The residue was crystallized

from methanol/water to provide the title compound as a mixture of E and Z oximes (yield: 82 mg, 35%). M.p. 95-99 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.03 (s, 3H), 4.07 (s, 3H), 5.57 (s, 2H), 6.94 (t, J = 9 Hz, 2H), 7.07 (dd, J = 9 Hz, 3 Hz, 2H), 7.24 (d, J = 9 Hz, 2H), 7.31-7.37 (m, 3H), 7.60-7.67 (m, 2H), 7.74 (s, 1H), 7.83 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 492 $(M+H)^+$. Anal. calc. for $C_{26}H_{22}FN_3O_4S$: C, 63.53; H, 4.51; N, 8.54. Found: C, 63.40; H, 4.51; N, 8.31.

Example 444

2-(3,4-Difluorophenyl)-4-(4-methylpentyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 255, substituting 1-bromo-4-methylpentane in place of 3,4-difluorobenzyl bromide (yield: 145 mg, 58%). M.p. 111-113 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.75 (d, 6H), 1.09 (m, 2H), 1.4 (m, 3H), 2.48 (m, 2H), 3.4 (s, 3H), 7.61 (m, 2H), 7.75 (d, 2H), 7.81 (m, 1H), 8.02 (s, 1H), 8.1 (d, 2H). MS (DCI-NH_3) m/z 447 $(M+H)^+$, 464 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{24}F_2N_2O_3S$: C, 61.87; H, 5.42; N, 6.27. Found: C, 61.76; H, 5.55; N, 6.11.

Example 445

2-(3,4-Difluorophenyl)-4-(3-methyl-1-butoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared as described in Example 384,-substituting 2-(3,4-difluorophenyl)-4-(3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 347) in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 248 mg, 42%). M.p. 149-151 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.8 (d, J = 6 Hz, 6H), 1.48 (m, 2H), 1.54 (m, 1H), 4.4 (t, 2H), 7.51 (m, 3H), 7.6 (m, 1H), 7.85 (m, 3H), 7.95 (d, J = 9 Hz, 2H), 8.21 (s, 1H). MS (DCI-NH_3) m/z 450 $(M+H)^+$, 467 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{21}F_2N_3O_4S$: C, 56.12; H, 4.71; N, 9.35. Found, C, 56.12; H, 4.67; N, 9.15.

Example 446

2-(2,2,2-Trifluoroethyl)-4-(2,2-dimethylpropoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The intermediate, 2-(2,2,2-trifluoroethyl)-4-hydroxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone prepared in Example 90C was reacted with 2,2-dimethyl-propanol to provide 2-(2,2,2-trifluoroethyl)-4-(2,2-dimethylpropoxy)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone according to the method of Example 90D. The product was oxidized with one equivalent of *meta*-chloroperoxybenzoic acid to provide the methyl sulfoxide. The sulfoxide was converted to the title compound according to the method of Example 68, substituting 2-(2,2,2-trifluoroethyl)-4-(2,2-dimethylpropoxy)-5-[4-(methylsulfinyl)phenyl]-3(2H)-pyridazinone for 2-(2,2,2-trifluoroethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfinyl)phenyl]-3(2H)-pyridazinone (yield: 125 mg, 53%). M.p. 123-124 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (s, 9H), 4.18 (s, 2H), 4.82 (q, J = 9 Hz, 2H), 4.84 (s, 2H), 7.70 (d, J = 9 Hz, 2H), 7.81 (s, 1H), 8.04 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 420 $(M+H)^+$. Anal. calc. for $C_{17}H_{20}F_3N_3O_4S$: C, 48.68; H, 4.80; N, 10.01. Found: C, 48.76; H, 4.77; N, 9.94.

Example 447

2-(2,2,2-Trifluoroethyl)-4-(3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 83, substituting 3-methyl-1-butanol in place of isopropanol (yield: 65 mg, 85%). M.p. 111-113 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (d, J = 6 Hz, 6H), 1.51 (m, 2H), 1.63 (m, 1H), 3.11 (s, 3H), 4.54 (t, J = 6 Hz, 2H), 4.83 (q, J = 9 Hz, 2H), 7.73 (d, J = 9 Hz, 2H), 7.82 (s, 1H), 8.05 (d, J = 9 Hz, 2H); MS (DCI-NH_3) m/z 419 $(M+H)^+$. Anal. calc. for $C_{18}H_{21}F_3N_2O_4S$: C, 51.66; H, 5.05; N, 6.69. Found: C, 51.91; H, 5.06; N, 6.56.

Example 448

2-(2,2,2-Trifluoroethyl)-4-(3-methylbutoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The intermediate, 2-(2,2,2-trifluoroethyl)-4-hydroxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone prepared in Example 90C was reacted with 3-methyl-1-butanol to provide 2-(2,2,2-trifluoroethyl)-4-(3-methylbutoxy)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone according to the method of Example 90D. The product was oxidized with one equivalent of *meta*-chloroperoxybenzoic acid to provide the methyl sulfoxide. The sulfoxide was converted to the title compound according to the method of Example 68, substituting 2-(2,2,2-trifluoroethyl)-4-(3-methylbutoxy)-5-[4-(methylsulfinyl)phenyl]-3(2H)-pyridazinone for 2-(2,2,2-trifluoroethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfinyl)phenyl]-3(2H)-pyridazinone (yield: 65 mg, 50%). M.p. 123-124 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (d, J = 6 Hz, 6H), 1.52 (q, J = 6 Hz, 2H), 1.60 (h, J = 7.5 Hz, 1H), 4.52 (t, J = 6 Hz, 2H), 4.83 (q, J = 9 Hz, 2H), 4.90 (s, 2H), 7.69 (d, J = 9 Hz, 2H), 7.82 (s, 1H), 8.04 (d, J = 9 Hz, 2H). MS (DCI-NH_3) m/z 420 $(M+H)^+$. Anal. calc. for $C_{17}H_{20}F_3N_3O_4S$: C, 48.68; H, 4.80; N, 10.01. Found: C, 48.86; H, 4.83; N, 9.92.

Example 449

2-(2,2,2-Trifluoroethyl)-4-(2-methylpropoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The intermediate, 2-(2,2,2-trifluoroethyl)-4-hydroxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone prepared in Example 90C was reacted with 2-methyl-1-propanol to provide 2-(2,2,2-trifluoroethyl)-4-(2-methylpropoxy)-5-[4-(methylthio)-phenyl]-3(2H)-pyridazinone according to the method of Example 90D. The product was oxidized with one equivalent of *meta*-chloroperoxybenzoic acid to provide the methyl sulfoxide. The sulfoxide was converted to the title compound according to the method of Example 68, substituting 2-(2,2,2-trifluoroethyl)-4-(2-methylpropoxy)-5-[4-(methylsulfinyl)phenyl]-3(2H)-pyridazinone for 2-(2,2,2-trifluoroethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfinyl)phenyl]-3(2H)-pyridazinone (yield: 120 mg, 40%). M.p. 170-172 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (d, J = 6 Hz, 6H), 1.9 (m, 1H), 4.3 (m, 2H), 4.82 (s, 2H), 4.88 (m, 2H), 7.70 (d, J = 9 Hz, 2H), 7.79 (s, 1H), 8.03 (d, J = 9 Hz, 2H); MS (DCI-NH_3) m/z 406 $(M+H)^+$. Anal. calc. for $C_{16}H_{18}F_3N_3O_4S$: C, 47.4; H, 4.47; N, 10.36. Found: C, 47.48; H, 4.36; N, 10.25.

Example 450

2-(2,3,3-Trifluoropropenyl)-4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The product of Example 4, 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone, was N-debenzylated by the method of Example 11 to provide 4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone. The intermediate was mixed with one equivalent of 1-methylsufonyl-oxy-2,3,3-trifluoro-2-propene, (Example 88A) in ethyl acetate, followed by one equivalent of cesium carbonate. The reaction mixture was heated to 50 °C for 5 hours. Aqueous work-up, followed by chromatography provided 2-(2,3,3-trifluoro-propenyl)-4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (650 mg, 63%). The product was oxidized with one equivalent of *meta*-chloroperoxybenzoic acid to provide the methyl sulfoxide which was converted to the title compound according to the method of Example 68, substituting 2-(2,3,3-trifluoropropenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfinyl)phenyl]-3(2H)-pyridazinone for 2-(2,2,2-trifluoroethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfinyl)phenyl]-3(2H)-pyridazinone (yield: 65 mg, 35%). M.p. 190-193°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.07 (s, 2H), 5.10 (dt, J = 21 Hz, J = 3 Hz, 2H), 7.05 (m, 4H), 7.19 (dd, J = 9 Hz, J = 6 Hz, 2H), 7.84 (s, 1H), 7.87 (t, J = 7.5 Hz, 1H). MS (ESI-NH_3) m/z 456 $(M-H)^+$. Anal. calc. for $C_{19}H_{12}F_5N_3O_3S$: C, 49.89; H, 2.64; N, 9.18. Found: C, 49.89; H, 2.73; N, 9.03.

Example 451

2-(4-Fluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 178, substituting 3-methyl-1,3-butandiol in place of 2-ethyl-1-hexanol (yield: 110 mg, 61%), M.p. 133-134 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.04 (s, 6H), 1.72 (t, J = 7 Hz, 2H), 3.29 (s, 3H), 4.32 (s, 1H), 4.53 (t, J = 7 Hz, 2H), 7.37 (t, J = 9 Hz, 2H), 7.66 (m, 2H), 7.90 (d, J = 9 Hz, 2H), 8.07 (d, J = 9 Hz, 2H), 8.19 (s, 1H). MS (APCI+) m/z 447 $(M+H)^+$; (APCI-) m/z 481 $(M+Cl)^-$. Anal. calc. for $C_{22}H_{23}FN_2O_5S \cdot 0.25\ H_2O$: C, 58.59; H, 5.25; N, 6.21. Found: C, 58.42; H, 5.00; N, 6.02.

Example 452

2-(3,4-Difluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 178, starting with 2-(3,4-difluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting 2-methyl-1,2-propandiol in place of 2-ethyl-1-hexanol (yield: 55 mg, 31%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.97 (s, 6H), 3.30 (s, 3H), 4.20 (s, 2H), 4.54 (s, 1H), 7.52 (m, 1H), 7.62 (m, 1H), 7.81 (m, 1H), 7.98 (d, J = 9 Hz, 2H), 8.05 (d, J = 9 Hz, 2H), 8.21 (s, 1H). MS (APCI+) m/z 451 $(M+H)^+$; (APCI-) m/z 485 $(M+Cl)^-$. Anal. calc. for $C_{21}H_{20}F_2N_2O_5S$: C, 55.99; H, 4.47; N, 6.21. Found: C, 56.00; H, 4.48; N, 5.87.

uExample 453

2-(3,4-Difluorophenyl)-4-methoxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was isolated from the reaction mixture in Example 233, as a product of oxidation of unreacted starting material (yield: 22 mg, 8%). M.p. 113-115 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.3 (s, 3H), 4.1 (s, 3H), 7.53 (m, 1H), 7.63 (m, 1H), 7.8 (m, 1H), 8.15 (d, 2H), 8.2 (s, 2H). MS (DCI-NH_3) m/z 393 $(M+H)^+$, 410 $(M+NH_4)^+$. Anal. calc. for $C_{18}H_{14}F_2N_2O_4S$: C, 55.10; H, 3.60; N, 7.14.

Example 454

2-(2,3,4,5,6-Pentafluorobenzyl)-4-(4-fluorophenyl)-5-[4-[(dimethylamino)-methylene]aminosulfonylphenyl]-3(2H)-pyridazinone

The title compound was isolated from the reaction mixture in Example 125, as a product resulting from a reaction with the solvent, N,N-dimethylformamide (yield: 53 mg, 16%). M.p. 194-196 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.05 (s, 3H), 3.17 (s, 3H), 5.49 (s, 2H), 6.97 (t, J = 9 Hz, 2H), 7.18 (dd, J = 9 Hz, 6 Hz, 2H), 7.20 (d, J = 9 Hz, 2H), 7.81 (s, 1H), 7.82 (d, J = 9 Hz, 2H), 8.14 (s, 1H). MS (DCI-NH_3) m/z 581 $(M+H)^+$. Anal. calc. for $C_{26}H_{18}F_6N_4O_3S$: C, 53.79; H, 3.12; N, 9.65. Found: C, 53.50; H, 3.24; N, 9.56.

Example 455

2-(2,4-Difluorobenzyl)-4-(4-fluorophenyl)-5-[4-[(dimethylamino)methylene]-aminosulfonylphenyl]-3(2H)-pyridazinone

The title compound was isolated from the reaction mixture in Example 124, as a product resulting from a reaction with the solvent, N,N-dimethylformamide (yield: 55 mg, 18%). M.p. 193-195 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.03 (s, 3H), 3.16 (s, 3H), 5.43 (s, 2H), 6.88 (m, 2H), 6.95 (t, J = 9 Hz, 2H), 7.18 (dd, J = 9 Hz, 6 Hz, 2H), 7.20 (d, J = 9 Hz, 2H), 7.52 (m, 1H), 7.81 (d, J = 9 Hz, 2H), 7.84 (s, 1H), 8.13 (s, 1H). MS (DCI-NH_3) m/z 527 $(M+H)^+$. Anal. calc. for $C_{26}H_{21}F_3N_4O_3S$: C, 59.30; H, 4.02; N, 10.64. Found: C, 59.08; H, 3.97; N, 10.48.

Example 456

2-(4-Fluorophenyl)-5-[4-(methylselenonyl)phenyl]-3(2H)-pyridazinone

446A. 4-Bromoselenoanisole

Freshly crushed magnesium turnings (6.1 g, 0.25 mol) were suspended with vigorous stirring in a solution of diethyl ether (360 mL) and 1,4-dibromobenzene (10 g, 0.04 mol). The solution was brought to reflux for 30 minutes, without initiation. Several crystals of iodine were added which initiated the reaction to a self-sustained reflux. The reflux was maintained as the remainder of the 1,4-dibromobenzene (49 g, 0.21 mol) was slowly added. The reaction was refluxed for an additional 2 hours after addition of the 1,4-dibromobenzene was completed. When nearly all of the magnesium turnings had been consumed, the yellow/gray heterogeneous solution was cooled to 23 °C, and selenium (19 g, 0.24 mol) was added in small portions via spatula so as to maintain a gentle reflux. The selenium that became stuck to the sides of the flask was washed in with additional diethyl ether. After addition, the solution was stirred for 20 minutes at 23 °C and then was cooled to 0 °C. A diethyl ether (20 mL) solution of methyl iodide (35.5 g, 0.25 mol) was slowly added dropwise to the reaction mixture. Upon completion of addition, the cooling bath was removed, and the solution stirred for 3 hours at 23 °C. The reaction solution was slowly poured into ice water/1 M HCl , and then the biphasic solution filtered through a glass wool plug. The ethereal layer was separated and the aqueous phase extracted twice more with diethyl ether. The combined ethereal extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide a semi-viscous orange oil. On standing overnight at -20 °C, large yellow needles formed. The residual oil was drawn off via pipette to provide 17 g (27%) of

crystalline product. (*J. Org. Chem.*, **1983**, *48*, 4169) ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (s, 3H), 7.12 (d, J = 8.7 Hz, 2H), 7.39 (d, J = 8.7 Hz, 2H). MS (APCI+) m/z 248 (Se_{76} M+H)$^+$, m/z 250 (Se_{78} M+H)$^+$, m/z 252 (Se_{80} M+H)$^+$, and m/z 254 (Se_{82} M+H)$^+$.

446B. <u>2,4-Bis(4-fluorophenyl)-5-[4-(methylseleno)phenyl]-3(2H)-pyridazinone</u>

The title compound was prepared according to the method of Example 228, substituting 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylseleno)phenyl]-3(2H)-pyridazinone [prepared according to the method of Example 194C, substituting 4-(methylseleno)benzeneboronic acid, (prepared according to the method of Example 1, substituting 4-bromoselenoanisole in place of 4-bromothioanisole) in place of 4-(methylthio)benzeneboronic acid] in place of 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone and substituting 4-fluorophenyl magnesium bromide in place of cyclohexylmagnesium chloride (yield: 44 mg, 69%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H), 6.98 (dd, J = 8.8, 8.8 Hz, 2H), 7.05 (d, J = 8.7 Hz, 2H), 7.17 (dd, J = 8.7, 8.7 Hz, 2H), 7.23-7.31 (m, 2H), 7.32 (d, J = 8.7 Hz, 2H), 7.65-7.72 (m, 2H), 8.00 (s, 1H). MS (APCI+) m/z 455 (M+H)$^+$.

446C. <u>2,4-Bis(4-fluorophenyl)-5-[4-(methylselenonyl)phenyl]-3(2H)-pyridazinone</u>

A stirred solution of the 2,4-bis(4-fluorophenyl)-4-(4-fluorophenyl)-5-[4-(methylseleno)phenyl]-3(2H)-pyridazinone (40 mg, 88.1 mmol) in methylene chloride (2 mL) was treated with 3-chloroperoxybenzoic acid (100 mg, 342 mmol, 57-86%) at 23 °C. After 2 hours, the reaction appeared to be only slightly more than 50% completed. Additional 3-chloroperoxybenzoic acid (80 mg, 274 mmol, 57-86%) was added. The reaction ran to completion over the next 16 hours of stirring at 23 °C. The solution was diluted with ethyl acetate and carefully shaken with a $NaHSO_3$ solution (two times) for several minutes to consume the excess 3-chloroperoxybenzoic acid. The ethyl acetate solution was subsequently washed with a saturated Na_2CO_3 solution (two times), water, and brine and dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was chromatographed (flash silica gel, acetone/methylene chloride/hexanes 2:2:1) to provide the product (yield: 40 mg, 93%). (*J. Chem. Soc., Chem. Commun.*, **1985**, 569). M.p. 110-150 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.32 (s, 3H), 6.91 (dd, J = 8.7, 8.7 Hz, 2H), 7.14-7.27 (m, 4H), 7.48 (d, J = 8.4 Hz, 2H), 7.65-7.73 (m, 2H), 7.97 (s, 1H), 8.00 (d, J = 8.4 Hz, 2H). MS (APCI+) m/z 487 (M+H)$^+$ and m/z 504 (M+NH_4)$^+$. Anal. calc. for

$C_{23}H_{16}F_2N_2O_3Se \cdot 0.5\ H_2O$: C, 55.88; H, 3.46; N, 5.66. Found: C, 55.60; H, 3.61; N, 5.29.

Example 457

2-(3,4-Difluorophenyl)-4-(3-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared as described in Example 62, starting with 4-(3-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting 3,4-difluorobromobenzene in place of 1-bromo-4-fluorobenzene (yield: 185 mg, 46.5%). M.p. 182-185 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 3.23 (s, 3 H), 6.98 (d, J = 9 Hz, 1H), 7.18 (m, 2H), 7.32 (m, 1H), 7.52 (d, J = 9 Hz, 2 H), 7.6 (m, 2H), 7.85 (m, 1 H), 7.9 (d, J = 9 Hz, 2H), 8.3 (s, 1 H). MS (DCI-NH_3) m/z 457 $(M+H)^+$, 474 $(M+NH_4)^+$.

Example 458

2-(4-Fluorophenyl)-4-(3-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared as described in Example 62, substituting 4-(3-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 135 mg, 34%). M.p. 199-201 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 3.24 (s, 3H), 6.98 (d, J = 9 Hz, 1H), 7.18 (m, 2H), 7.32 (m, 1H), 7.39 (t, 1H), 7.54 (d, J = 9 Hz, 2 H), 7.71 (m, 2H), 7.91(d, J = 9 Hz, 2 H), 8.27 (s, 1 H). MS (DCI-NH_3) m/z 439 $(M+H)^+$, 456 $(M+NH_4)^+$.

Example 459

2-(3,4-Difluorophenyl)-4-(2-hydroxy-2-methylpropoxy)-5-[4-(aminosulfonyl)-phenyl]-3(2H)-pyridazinone

2-(3,4-Difluorophenyl)-4-(2-hydroxy-2-methylpropoxy)-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone (Example 452) is converted to the title sulfonamide according to the method of Example 384.

Example 460

2-(3,4-Difluorophenyl)-4-(2-oxo-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A solution of 2-(3,4-difluorophenyl)-4-hydroxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (378 mg, 1 mmol), Ph_3P (524 mg, 2 mmol) and acetol (74 mg, 1 mmol) in THF (25 mL) at room temperature was treated dropwise with a solution of DIAD (0.4 mL, 2 mmol) in THF (5 mL). The mixture was stirred at room temperature for 6 hours and concentrated *in vacuo*. The residue was chromatographed (silica gel, 1:1 hexanes-ethyl acetate) to provide the desired product (yield: 205 mg, 48%). M.p. 169-170 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 2.08 (s, 3H), 3.30 (s, 3H), 5.30 (s, 2H), 7.48 (m, 1H), 7.62 (q, J = 10 Hz, 1H), 7.75 (m, 1H), 7.94 (d, J = 9 Hz, 2H), 8.05 (d, J = 9 Hz, 2H), 8.21 (s, 1H). MS (APCI+) m/z 435 $(M+H)^+$, (APCI-) m/z 469 $(M+Cl)^-$. Anal. calc. for $C_{20}H_{16}F_2N_2O_5S{\cdot}0.75H_2O$: C, 53.62; H, 3.93; N, 6.25. Found: C, 53.26; H, 3.61; N, 6.08.

Example 461

2-(3,4-Difluorophenyl)-4-[2-(methoxyimino)propoxy]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A mixture of 2-(3,4-difluorophenyl)-4-(2-oxo-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone from Example 460 (150 mg, 0.3 mmol) in H_2O (10 mL) and dioxane (20 mL) was treated with methoxylamine

hydrochloride (84 mg, 1 mmol) and sodium acetate trihydrate (138 mg, 1 mmol). The mixture was stirred at room temperature for 6 hours. The reaction mixture was extracted with ethyl acetate and purified by column chromatography (silica gel, 1:1 hexanes-ethyl acetate) to provide the title compound (yield: 20 mg, 15%). M.p. 143-145 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.63 (s, 3H), 3.30 (s, 3H), 3.74 (s, 3H), 4.93 (s, 2H), 7.54 (m, 1H), 7.65 (q, J = 10 Hz, 1H), 7.82 (m, 1H), 7.92 (d, J = 9 Hz, 2H), 8.07 (d, J = 9 Hz, 2H), 8.24 (s, 1H). MS (APCI+) m/z 464 $(M+H)^+$; (APCI-) m/z 498 $(M+Cl)^-$. Anal. calc. for $C_{21}H_{19}F_2N_3O_5S$: C, 54.42; H, 4.13; N, 9.06. Found: C, 54.33; H, 3.93; N, 8.92.

Example 462

(S)-2-(3,4-Difluorophenyl)-4-(3-hydroxy-2-methylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

462A (R)-3-*t*-Butoxy-2-methyl-1-propanol

A solution of (S)-(+)-methyl 3-hydroxy-2-methylpropionate (1.18 g, 10 mmol) in t-butyl acetate (30 mL) was treated with 70% $HClO_4$ (0.1 mL), and the reaction mixture was left at room temperature in a tighthly closed flask for 24 hours. The mixture was poured into a saturated solution of sodium bicarbonate and extracted with diethyl ether. The ether was removed *in vacuo* and the residue was dissolved in THF (50 mL). To the resulting solution was added sodium borohydride (925 mg, 25 mmol) and at 55 °C dropwise methanol (10 mL). The reaction was continued at 55 °C for 1 hour, then cooled to room temperature, acidified with 10% citric acid to pH 5 and extracted with ethyl acetate. The acetate extract was washed with water, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (silica gel, 2:1 hexanes-ethyl acetate) to provide (R)-3-*t*-butoxy-2-methyl-1-propanol (yield: 1 g, 68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, J = 7 Hz, 3H), 1.20 (s, 9H), 2.03 (m, 1H), 3.30 (t, J = 12 Hz, 1H), 3.53 (dd, J = 12 Hz, 4.5 Hz, 1H), 3.70 (m, 2H). MS (DCI-NH_3) m/z 164 $(M+NH_4)^+$.

462B (S)-2-(3,4-Difluorophenyl)-4-(3-*t*-butoxy-2-methylpropoxy)-5-[4-(methylsulphonyl)phenyl]-3(2H)-pyridazinone

To a solution 2-(3,4-difluorophenyl)-4-hydroxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (378 mg, 1 mmol), Ph_3P (524 mg, 2 mmol) and the above

alcohol, (R)-3-*t*-butoxy-2-methyl-1-propanol (146 mg, 1 mmol) in THF (25 mL) at room temperature was added dropwise a solution of DIAD (0.4 mL, 2 mmol) in THF (5 mL). The mixture was then stirred at room temperature for 6 hours and concentrated *in vacuo*. The residue was passed through a silica gel pad (hexanes-ethyl acetate as an eluent) to provide 550 mg of roughly purified (S)-2-(3,4-difluorophenyl)-4-(3-*t*-butoxy-2-methylpropoxy)-5-[4-(methylsulphonyl)phenyl]-3(2H)-pyridazinone, still contaminated with reduced DIAD. MS (APCI+) m/z 507 $(M+H)^+$; (APCI-) m/z 541 $(M+Cl)^-$.

462C <u>(S)-2-(3,4-Difluorophenyl)-4-(3-hydroxy-2-methylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone</u>

A mixture of the above product (100 mg, ~0.2 mmol) in TFA (5 mL) was stirred at room temperature for 24 hours and then concentrated *in vacuo*. The residue was neutralized with saturated $NaHCO_3$ and extracted with ethyl acetate. Purification by column chromatography (silica gel, 1:2 hexanes-ethyl acetate) provided the title compound (yield: 51 mg, 56%). ^1H NMR (300 MHz, DMSO-d_6) δ 0.75 (d, J = 7 Hz, 3H), 1.81 (septet, J = 7 Hz, 1H), 3.21 (d, J = 6 Hz, 2H), 3.30 (s, 3H), 4.29 (dd, J = 12 Hz, 6 Hz, 1H), 4.40 (dd, J = 12 Hz, 6 Hz, 1H), 4.48 (br s, 1H), 7.52 (m, 1H), 7.61 (m, 1H), 7.80 (m, 1H), 7.91 (d, J = 9 Hz, 2H), 8.07 (d, J = 9 Hz, 2H), 8.20 (s, 1H). MS (APCI+) m/z 451 $(M+H)^+$; (APCI-) m/z 485 $(M+Cl)^-$. Anal. calc. for $C_{21}H_{20}F_2N_2O_5S$: C, 55.99; H, 4.47; N, 6.21. Found: C, 55.65; H, 4.65; N, 5.92.

Example 463

<u>(R)-2-(3,4-Difluorophenyl)-4-(3-hydroxy-2-methylpropoxy)-5-[4-(methylsulfonyl)-phenyl]pyridazinone</u>

The desired material was prepared according to the procedure of Example 462 starting with (R)-(-)-methyl 3-hydroxy-2-methylpropionate in place of (S)-(-)-methyl 3-hydroxy-2-methylpropionate (yield: 65 mg, 61%). ^1H NMR (300 MHz, DMSO-d_6) δ 0.75 (d, J = 7 Hz, 3H), 1.81 (septet, J = 7 Hz, 1H), 3.21 (t, J = 6 Hz, 2H), 3.30 (s, 3H), 4.29 (dd, J = 6 Hz and 12 Hz, 1H), 4.40 (dd, J = 6 Hz and 12 Hz, 1H), 4.49 (t, J = 6 Hz, 1H), 7.52 (m, 1H), 7.61 (m, 1H), 7.80 (m, 1H), 7.91 (d, J = 9 Hz, 2H), 8.07 (d, J = 9 Hz, 2H), 8.20 (s, 1H). MS (APCI+) m/z 451 $(M+H)^+$; (APCI-) m/z

485 $(M+Cl)^-$. Anal. calc. for $C_{21}H_{20}F_2N_2O_5S$: C, 55.99; H, 4.47; N, 6.21. Found: C, 55.62; H, 4.52; N, 6.06.

Example 464

(S)-2-(3,4-Difluorophenyl)-4-(3-hydroxy-2-methylpropoxy)-5-[4-(aminosulfonyl)-phenyl]-3(2H)-pyridazinone

To a solution of (S)-2-(3,4-difluorophenyl)-4-(3-hydroxy-2-methylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone from Example 462 (450 mg, ~0.9 mmol) and DBAD (207 mg, 0.9 mmol) in THF (25 mL) at -78 °C was added dropwise 1 M lithium bis(trimethylsilyl)amide solution in THF (3 mL, 3 mmol). The resulting mixture was stirred at -78 °C for 2 hours. The mixture was warmed to room temperature and 1N NaOH was added (5 mL, 5 mmol). After 12 hours, at room temperature, sodium acetate trihydrate (2.76 g, 20 mmol) and H_2O (10 mL) followed by hydroxylamine-O-sulphonic acid (2 g, 15 mmol) were added and the mixture was stirred at room temperature for 5 hours. The product was extracted with ethyl acetate and purified by chromatography (silica gel, 1:2 hexanes-ethyl acetate) to provide the desired intermediate (yield: 160 mg, 35%). MS (APCI+) m/z 508 $(M+H)^+$; (APCI-) m/z 542 $(M+Cl)^-$.

TFA (5 mL) was added to the above intermediate and the resulting solution was stirred at room temperature for 24 hours. The TFA was removed *in vacuo*, and the residue was neutralized with saturated $NaHCO_3$ and extracted with ethyl acetate. The organic extract was dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and the residue was chromatographed (silica gel, 1:2 hexanes-ethyl acetate) to provide the title compound (yield: 50 mg, 33%). ^1H NMR (300 MHz, DMSO-d_6) δ 0.76 (d, J = 7 Hz, 3H), 1.81 (sextet, J = 7 Hz, 1H), 3.22 (t, J = 6 Hz, 2H), 4.28 (dd, J = 12 Hz, 6 Hz, 1H), 4.40 (dd, J = 12 Hz, 6 Hz, 1H), 4.50 (t, J = 6 Hz, 1H), 7.51 (m, 3H), 7.61 (m, 1H), 7.80 (m, 1H), 7.84 (d, J = 9 Hz, 2H), 7.95 (d, J = 9 Hz, 2H), 8.20 (s, 1H). MS (APCI+) m/z 452 $(M+H)^+$; (APCI-) m/z 486 $(M+Cl)^-$.

Example 465

(R)-2-(3,4-Difluorophenyl)-4-(3-hydroxy-2-methylpropoxy)-5-[4-(aminosulfonyl)-phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the procedure of Example 464 starting with (R)-2-(3,4-difluorophenyl)-4-(3-hydroxy-2-methylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of (S)-2-(3,4-difluorophenyl)-4-(3-hydroxy-2-methylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 30 mg, 20%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.76 (d, J = 7 Hz, 3H), 1.81 (sextet (J = 7 Hz, 1H), 3.22 (t, J = 6 Hz, 2H), 4.28 (dd, J = 6 Hz and 12 Hz, 1H), 4.40 (dd, J = 6 Hz and 12 Hz, 1H), 4.50 (t, J = 6 Hz, 1H), 7.51 (m, 3H), 7.61 (m, 1H), 7.80 (m, 1H), 7.84 (d, J = 9 Hz, 2H), 7.95 (d, J = 9 Hz, 2H), 8.20 (s, 1H). MS (APCI+) m/z 452 $(M+H)^+$; (APCI-) m/z 486 $(M+Cl)^-$. Anal. calc. for $C_{20}H_{19}F_2N_3O_5S$: C, 53.21; H, 4.24; N, 9.30. Found: C, 53.45; H, 5.53; N, 9.50.

Example 466

2-(4-Fluorophenyl)-4-(4-hydroxy-3-methylbutoxy)-5-[4-(methylsulphonyl)phenyl]-3(2H)-pyridazinone.

The title compound was prepared according to the method of Example 178, substituting 2-methyl-1,4-butanediol in place of 2-ethyl-1-hexanol and separating the regioisomeric products by preparative TLC using Silica Gel with ethyl acetate:hexanes (4/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, J = 8.1 Hz, 3H), 1.48-1.87 (m, 4H), 3.13 (s, 3H), 3.41 (dd, J = 6.3, 13.5 Hz, 1H), 3.46 (dd, J = 6.3, 13.5 Hz, 1H), 4.48-4.63 (m, 2H), 7.15-7.24 (m, 2H), 7.58-7.66 (m, 2H), 7.79 (d, J=10.5 Hz, 2H), 7.91 (s, 1H), 8.07 (d, J = 10.5 Hz, 2H). MS (APCI+) m/z 447 $(M+H)^+$.

Example 467

2-(3,4-difluorophenyl)-4-(3-oxobutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound is prepared according to the method of Example 460 ßsubstituting 4-hydroxy-2-butanone in place of acetol. (yield: 95.0 mg, 21%). M.p. 134-135 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.06 (s, 3H), 2.81 (t, J = 9 Hz, 2H), 3.13 (s, 3H), 4.75 (t, J = 9 Hz, 2H), 7.30 (m, 1H), 7.45 (m, 1H), 7.58 (m, 1H), 7.73 (d, J = 9

Hz, 2H), 7.89 (s, 1H), 8.05 (d, J = 9 Hz, 2H) . MS (DCI-NH_3) m/z 449 $(M+H)^+$, 466 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{18}F_2N_2O_5S$: C, 56.25; H, 4.02; N, 6.25. Found: C, 55.97; H, 4.17; N, 6.11.

Example 468

2-(4-Fluorophenyl)-4-(3-oxobutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound is prepared according to the method of Example 460 starting with 2-(4-fluorophenyl)-4-hydroxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(3,4-difluorophenyl)-4-hydroxy-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone and substituting 4-hydroxy-2-butanone in place of acetol. (yield: 85.0 mg, 20%). M.p. 133-136 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.04 (s, 3H), 2.80 (t, J = 9 Hz, 2H), 3.13 (s, 3H), 4.76 (t, J = 9 Hz, 2H), 7.20 (t, J = 9 Hz, 2H), 7.55 (m, 2H), 7.75 (d, J = 9 Hz, 2H), 7.91 (s, 1H), 8.05 (d, J = 9 Hz, 2H) . MS (DCI-NH_3) m/z 431 $(M+H)^+$, 448 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{19}FN_2O_5S$: C, 58.60; H, 4.42; N, 6.52. Found: C, 58.87; H, 4.55; N, 6.51.

Prostaglandin Inhibition Determination

Compound Preparation and Administration

For oral administration, test compounds were suspended on the day of use in 100% polyethyleneglycol (PEG 400) with a motorized homogenizer equipped with a Teflon-coated pestle (TRI-R Instrument, Jamaica, NY).

To compare the mean responses of the treatment groups, analysis of variance was applied. Percent inhibition values were determined by comparing the individual treatment mean values to the mean of the control group. Linear regression was used to estimate IC_{50}'s/ED_{50}'s in appropriate assays.

EIA Determination of Prostaglandins

EIA reagents for prostaglandin determination were purchased from Perseptive Diagnostics, (Cambridge, MA). Prostaglandin E_2 (PGE_2) levels in lavage fluids were determined after the samples were dried under nitrogen and

reconstituted with assay buffer. PGE_2 levels in enzyme assays or cell culture media were measured against standards prepared in the same milieu. The immunoassays were conducted as recommended by the manufacturer. The EIA was conducted in 96 well microtiter plates (Nunc Roskilde, Denmark) and optical density was measured using a microplate reader (Vmax, Molecular Devices Corp., Menlo Park, CA).

Recombinant Human PGHS-1 and PGHS-2 Enzyme Assays

Inhibition of prostaglandin biosynthesis *in vitro* was evaluated using recombinant human Cox-1 (r-hu Cox1) and Cox-2 (r-hu Cox2) enzyme assays. Representative compounds dissolved in DMSO (3.3% v/v) were preincubated with microsomes from recombinant human PGHS-1 or PGHS-2 expressed in the baculovirus/Sf9 cell system (Gierse, J. K., Hauser,S. D., Creely, D. P., Koboldt, C., Rangwala, S., H., Isakson, P. C., and Seibert, K. Expression and selective inhibition of the constituitive and inducible forms of cyclooxygenase , *Biochem J.* 1995, 305: 479.), together with the cofactors phenol (2 mM) and hematin (1 μM) for 60 minutes prior to the addition of 10 μM arachidonic acid. The reaction was allowed to run for 2.5 minutes at room temperature prior to quenching with HCl and neutralization with NaOH. PGE_2 production in the presence and absence of the drug was determined by EIA analysis. The EIA was conducted in 96 well microtiter plates (Nunc Roskilde, Denmark) and optical density was measured using a microplate reader (Vmax, Molecular Devices Corp., Menlo Park, CA). EIA reagents for prostaglandin determination were purchased from Perseptive Diagnostics (Cambridge, MA). PGE_2 levels were measured against standards prepared in the same milieu. The immunoassays were conducted as recommended by the manufacturer.

The data illustrating the inhibition of prostaglandin biosynthesis *in vitro* by compounds of this invention is shown in Table 1. The compounds are designated by the Example Number. Column 2 shows Cox-1 percent inhibition at the particular micromolar dose level and Column 3 shows Cox-2 percent inhibition at the particular nanomolar dose level. Values for Cox-2 inhibition that are parenthetical indicate IC_{50} values.

SEE ATTACHED TABLE

Table 1

Example Numbers	RHUCX1 % Inh. at Dose (μM)	RHUCX2 % Inh. at Dose (μM)
10	2 @ 100	(0.014)
12	0 @ 100	97 @ 10 77 @ 1 9 @ 0.1
20	10 @ 100	86 @ 0.1 9 @ 0.01
21	19 @ 100	(0.92)
22	25 @ 100	91 @ 0.03 35 @ 0.01
23	0 @ 100	68 @ 0.1 27 @ 0.01
24	60 @ 100 0 @ 10	99 @ 1 61 @ 0.1 45 @ 0.01
25	1 @ 100	93 @ 1 66 @ 0.1
26	10 @ 100	91 @ 1 44 @ 0.1 44 @ 0.01
32	20 @ 100	96 @ 1 83 @ 0.1
34	16 @ 100	(0.92)

35	34 @ 100	(0.017)
36	21 @ 10	(0.57)
39	0 @ 100	(0.44)
40	76 @ 10 69 @ 1	97 @ 1 89 @ 0.1
41	13 @ 100	49 @ 1 17 @ 0.1
42	0 @ 100	99 @ 1 92 @ 0.1
43	8 @ 100	100 @ 1 96 @ 0.1
45	5 @ 100	85 @ 1 63 @ 0.1
48	0 @ 100	73 @ 1 2 @ 0.1
50	23 @ 100	99 @ 1 59 @ 0.1
52	32 @ 10	99 @ 1 83 @ 0.1
53	10 @ 100	99 @ 1 77 @ 0.1
54	0 @ 100	95 @ 1 58 @ 0.1
58	0 @ 100	(0.95)

60	7 @ 100	100 @ 1,000
62	6 @ 100	(0.624)
64	68 @ 1	34@ 1 36@ 0.1
65	13 @ 100	98 @ 1 65 @ 0.1
68	32 @ 100	(0.297)
69	2 @ 100	88 @ 1 29 @ 0.1 30 @ 0.01
72	0 @ 100	65 @ 1 18 @ 0.1
73	9 @ 100	(1.34)
74	11 @ 100	86 @ 1 75 @ 0.1
77	35 @ 100	82 @ 10 39 @ 1
80	41 @ 10 37 @ 1	(0.064)
81	6 @ 100	97 @ 1 44 @ 0.1
84	49 @ 10 9 @ 1	87 @ 0.3

88	0 @ 100	97 @ 1,000 35 @ 0.1
89	62 @ 30 40 @ 10	(0.35)
97	35 @ 100	(0.332)
100	62 @ 10 65 @ 1	100 @ 10 61 @ 0.1
105	85 @ 1	98 @ 1 52 @ 0.1
106	19 @ 200	(0.135)
107	88 @ 10 50 @ 1	86 @ 1 36 @ 0.1
108	0 @ 100	(0.279)
109	6 @ 100	(0.147)
110	5 @ 100	93 @ 1 50 @ 0.1
111	13 @ 100	(0.052)
112	5 @ 100	(0.136)
118	31 @ 100	72 @ 0.1 17 @ 0.01
119	(0.178)	(0.027)
120	15 @ 100	97 @ 1 45 @ 0.1
121	0 @ 100	(0.005)

122	1 @ 100	(0.285)
124	26 @ 100	(0.044)
127	50 @ 10 30 @ 1	74 @ 1 51 @ 0.1
128	14 @ 100	(0.477)
132	93 @ 1	88 @ 1 43 @ 0.1
133	23 @ 100	(0.358)
134	54 @ 100 35 @ 10	(0.053)
140	(3.06)	(0.022)
141	55 @ 100 62 @ 10	99 @ 1 95 @ 0.1
142	80 @ 10 53 @ 1	96 @ 1 45 @ 0.1 32 @ 0.01
143	62 @ 100 43 @ 10	(0.076)
144	(0.058)	88 @ 1 78 @ 0.1 65 @ 0.01
145	(0.238)	86 @ 0.1 56 @ 0.01
146	82 @ 10 53 @ 1	100 @ 1 73 @ 0.1

147	(0.067)	100 @ 1 64 @ 0.1 0 @ 0.03
149	45 @ 10 40 @ 1	(0.003)
150	56 @ 100 39 @ 10	100 @ 0.1
153	54 @ 100 35 @ 10	(0.062)
154	(0.126)	(0.018)
165	0 @ 100	(1.08)
166	3 @ 100	(0.199)
168	0 @ 100	85 @ 1 93 @ 0.1
171	0 @ 100	82 @ 10 74 @ 1 61 @ 0.1
178	6 @ 100	92 @ 1,000 34 @ 10
180	8 @ 100	78 @ 1 48 @ 0.1
182	(5.01)	(0.07)
183	25 @ 100	97 @ 1 51 @ 0.1
187	2 @ 100	(0.094)

188	18 @ 100	(0.526)
190	(1.88)	(0.134)
194	35 @ 100	90 @ 10 73 @ 1 72 @ 0.1
198	10 @ 100	68 @ 1 23 @ 0.1
207		97 @ 1 81 @ 0.1
209	0 @ 100	79 @ 1 55 @ 0.1 40 @ 0.01
213	0 @ 100	(0.812)
219	20 @ 100	90 @ 1 75 @ 0.1
220	51 @ 100 38 @ 1	96 @ 1 90 @ 0.1
226	0 @ 100	(1.09)
228	7 @ 100	(0.209)
230	4 @ 100	(0.215)
231	7 @ 100	90 @ 1 68 @ 0.1
232	23 @ 100	(0.024)
234	0 @ 100	(0.328)

235	22 @ 100	(0.21)
237	54 @ 10 44 @ 1	89 @ 0.1
240	14 @ 100	(0.297)
241	0 @ 100	(0.028)
245	9 @ 100	(1.38)
246	0 @ 100	(0.054)
247	72 @ 10 55 @ 1	99 @ 10 71 @ 1 51 @ 0.1
248	13 @ 100	(0.08)
249	6 @ 100	98 @ 1 68 @ 0.1 43 @ 0.01
252	0 @ 100	87 @ 0.1 26 @ 0.01
253	77 @ 100 29 @ 10	(0.272)
254	7 @ 100	84 @ 1 48 @ 0.1
256	0 @ 100	(0.134)
257	0 @ 100	(0.04)
260	8 @ 100	2 @ 10
261	0 @ 200	(0.161)

262	15 @ 100	(0.432)
263	1 @ 100	85 @ 10 76 @ 1 53 @ 0.1
265	8 @ 100	53 @ 10 48 @ 1 33 @ 0.1
272	0 @ 100	70 @ 1 55 @ 0.1
273	16 @ 100	54 @ 10 42 @ 1
278	36 @ 100	96 @ 1 91 @ 0.1
279	0 @ 100	60 @ 1 31 @ 0.1
281	7 @ 100	71 @ 1 52 @ 0.1 47 @ 0.01
283	0 @ 100	90 @ 10 71 @ 1 54 @ 0.1
287	0 @ 100	93 @ 10 79 @ 1 25 @ 0.1
314	7 @ 100	51 @ 10 4 @ 1

374	2 @ 100	(0.02)
375	46 @ 100 31 @ 10	(0.18)
376	12 @ 100	(0.027)
381	0 @ 100	(0.188)
384	82 @ 100 49 @ 10	99 @ 1 78 @ 0.1
386	58 @ 100 47 @ 1	83 @ 1 63 @ 0.1 58 @ 0.01
387	57 @ 10 60 @ 1	76 @ 1 65 @ 0.1 56 @ 0.01
388	74 @ 10 36 @ 1	(0.049)
390	88 @ 10 45 @ 1	99 @ 10 72 @ 1 60 @ 0.1
392	56 @ 100 35 @ 10	82 @ 0.1 65 @ 0.01
393	15 @ 100	85 @ 1 58 @ 0.1
394	86 @ 100 38 @ 10	94 @ 1 64 @ 0.1 20 @ 0.01

395	91 @ 100 35 @ 10	93 @ 1 77 @ 0.1 34 @ 0.01
396	22 @ 100	(0.059)
397	25 @ 100	93 @ 1 58 @ 0.1 39 @ 0.01
398	26 @ 100	(0.202)
400	27 @ 100	(0.142)
401	(0.753)	96 @ 1 62 @ 0.1 48 @ 0.01
402	89 @ 1	(0.221)
403	(150.76)	92 @ 1 64 @ 0.1 36 @ 0.01
404	77 @ 100 47 @ 10	92 @ 0.1 57 @ 0.01
405	90 @ 100 61 @ 10	(0.198)
406	23 @ 100	100 @ 1 64 @ 0.1 18 @ 0.01
407	32 @ 100	(0.17)
408	0 @ 100	(0.279)

410	48 @ 100 1 @ 10	67 @ 0.035 47 @ 0.017
411	96 @ 10 81 @ 1	(0.009)
412	31 @ 100	(0.002)
413	0 @ 100	(0.11)
414	0 @ 100	87 @ 1 76 @ 0.1
418	33 @ 100	85 @ 1 52 @ 0.1 53 @ 0.025
419	12 @ 100	(0.1)
420	29 @ 100	(0.323)
421	(0.269)	92 @ 1 81 @ 0.1 38 @ 0.01
422	53 @ 100 82 @ 10 76 @ 1	52 @ 1 37 @ 0.1
423	0 @ 100	87 @ 1 68 @ 0.1 36 @ 0.01
424	7 @ 100	75 @ 1 58 @ 0.1 33 @ 0.01
425	12 @ 100	69 @ 0.1 31 @ 0.01

426	1 @ 100	(0.057)
434	0 @ 100	(0.081)
437	16 @ 100	(0.124)
438	0 @ 100	(0.127)
440	20 @ 100	84 @ 1 59 @ 0.1 22 @ 0.01
442	55 @ 100	90 @ 0.1 56 @ 0.01
443	35 @ 100	86 @ 0.1 74 @ 0.01
444	0 @ 100	83 @ 1 62 @ 0.1 14 @ 10
445	(56.62)	(0.069)
446	0 @ 200	(0.373)
447	0 @ 100	90 @ 1 57 @ 0.1 35 @ 0.01
449	5 @ 200	(0.129)
450	29 @ 100	87 @ 1 40 @ 0.1 22 @ 0.01
451	10 @ 100	43 @ 1 22 @ 0.1

452	14 @ 100	15 @ 1

IL-1ß Induced PGE_2 Production in WISH Cells

Human amnionic WISH cells were grown to 80% confluence in 48 well plates. Following removal of the growth medium and two washings with Gey's Balanced Salt Solutn, 5 ng IL-1ß/ml (UBI, Lake Placid, NY) was added to the cells with or without test compound in DMSO (0.01% v/v) in Neuman-Tytell Serumless Medium (GIBCO, Grand Island, NY). Following an 18 hour incubation to allow for the maximal induction of PGHS-2, the conditioned medium was removed and assayed for PGE_2 content by EIA analysis as described above.

Monocyte U937 (ATCC, Rockville, MD) cells were grown in a similar fashion to the WISH cells. After incubation, the conditioned medium was removed and assayed for Cox-1 content by EIA analysis as described above.

The data illustrating the inhibition of prostaglandin biosynthesis *in vitro* by compounds of this invention is shown in Table 2. U937 values indicate Cox-1 percent inhibition at the particular micromolar dose level while partenthetical values indicate IC_{50} values. WISH cell values indicate percent inhibition at the particular micromolar dose level while parenthetical values indicate IC_{50} values.

Human Whole Platelet Cyclooxygenase-1 Assay (HWCX)

Blood from normal healthy volunteers is collected into tubes containing ACD (acid citrate dextrose) as the anticoagulant. This blood is centrifuged at 175 x g to prepare platelet rich plasma. The platelet rich plasma is then centrifuged at 100 x g to pellet the white blood cells, leaving the platelets in the supernatant. The supernatant is layered on a cushion of 0.7 mL of 10% bovine serum albumin in Tyrodes solution (Gibco; Grand Island, NY) and then centrifuged at 1000 x g. The resulting supernatant from this centrifugation is then removed and 11 mL of Tyrodes solution is added to the remaining pellet of platelets. The platelets are then aliquoted at 120 µl into a 96 well plate. Experimental compounds are added and allowed to pre-incubate for 10 minutes. At the end of this pre-incubation period, the calcium ionophore A23187 is added to a final concentration of 8.8 µM and the incubation is continued for ten minutes. The reaction is stopped by adding cold 6 mM EDTA, the incubation mixture is centrifuged at 220 x g, and the

supernatants are then analyzed for thromboxane using a commercial kit from Cayman Chemical (Ann Arbor, MI).

SEE ATTACHED TABLE

Table 2

Example Numbers	U937 % Inhib. at Dose (μM)	HWPX % Inhib. at Dose (μM)	Wish % Inhib. at Dose (μM)
10		(4.1)	(0.014)
20	33 @ 1		(0.001)
24	(0.19)		(0.007)
43		86 @ 10 9 @ 1	(0.008)
53		78 @ 10 8 @ 1	90 @ 0.1 44 @ 0.01
65			(0.02)
69		(1.14)	(0.02)
72		(25)	(0.072)
75		84 @ 10 0 @ 3	(0.001)
77		(8.8)	(0.126)
85			(0.47)
86			52 @ 1 47 @ 0.01
89	(3.8)	(2.1)	(0.05)
100		(0.13)	(0.02)
102			(0.05)
105		62 @ 1	(0.018)
106		(17.5)	(0.03)
108		(8)	(0.097)
109		(2.693)	(0.018)
119		(0.076)	(0.001)

120		74 @ 3 58 @ 1	(0.025)
121			(0.041)
123		90 @ 1 29 @ .1	(0.001)
126			(0.05)
129			(0.04)
132			100 @ 0.1 36 @ 0.01
140		(0.773)	(0.01)
141		56 @ 0.3	(0.004)
142		(7.53)	(0.088)
143			(0.007)
145		72 @ 1 30 @ .3	(0.009)
146		84 @ 10 46 @ 3	(0.044)
147		84 @ 0.3	(0.029)
148		51 @ 0.3	(0.042)
149		89 @ 10 34 @ 3	(0.03)
152			(0.029)
153		(2.95)	(0.046)
154		81 @ .3 48 @ .1	100 @ 0.1 69 @ 0.01
160		(7.2)	(0.03)
162			(0.034)
165		(1.9)	(0.030)
166		(9.4)	(0.02)
168		47 @ 1	(0.009)
171			90 @ 1 56 @ 0.1
187		(12.6)	(0.015)

189		31 @ 100	(0.041)
190		(9.96)	(0.03)
191			(0.06)
194		(28.09)	(0.069)
198			(0.184)
203			77 @ 1 23 @ 0.1
207			(0.068)
228		(19.6)	(0.086)
241			(0.0474)
243			(0.03)
244		(3.67)	(0.019)
245			(0.046)
246			(0.02)
247		(7.76)	(0.02)
248		82 @ 30 17 @ 10	(0.005)
252			(0.044)
256		(4.7)	(0.028)
261		(34)	(0.099)
271			52 @ 1 15 @ 0.1
278			(0.07)
279			(0.391)
287			(0.16)
317			(0.027)
320		29 @ 3	78 @ .1 15 @ .01
321			50 @ 0.01
322			(0.026)
323			57 @ 0.01
324			(0.047)

325		(2.3)	(0.04)
326			(0.05)
330		(16.7)	(0.005)
335			(0.023)
338		(14.93)	(0.004)
339		(0.393)	(0.026)
343		(0.191)	(0.016)
344			(0.1)
345			(0.03)
349		34 @ 100	(0.041)
352		(5.5)	(6.048)
358			69 @ 1 0 @ 0.1
366		(1.615)	(0.002)
367		50 @ 1 8 @ .3	(0.018)
368		(13.7)	64 @ 0.03 33 @ 0.01
370		(8.4)	(0.02)
374			(0.03)
381		31 @ 30 91 @ 100	(0.075)
385		(2.18)	(0.023)
388		0 @ .3	(0.032)
392		(1.95)	(0.02)
394			(0.019)
396		(12.7)	(0.02)
397		(13.8)	(0.04)
399			82 @ 0.1 39 @ 0.03
400		(0.3)	(0.026)
401		(0.32)	(0.017)

403		(0.902)	(0.018)
404		(0.337)	96 @ 0.1 58 @ 0.01
406		(1.61)	(0.026)
408			(0.029)
410			(0.053)
414			54 @ 1 46 @ 0.1
418		(14.25)	(0.25)
430		34 @ 10 89 @ 100	(0.054)
442			(0.42)
445		100 @ 100 22 @ 1 0	(0.025)
446		(24.4)	(0.02)
449		(40)	(0.089)
450			(0.05)
451		(25.6)	(0.15)
452			56 @ 1 1 @ 0.1

Carrageenan Induced Paw Edema (CPE) in Rats

Hindpaw edema was induced in male rats as described by Winter *et al.*, *Proc. Soc. Exp. Biol. Med.*, **1962**, *111*, 544. Briefly, male Sprague-Dawley rats weighing between 170 and 190 g were administered test compounds orally 1 hour prior to the subplantar injection of 0.1 ml of 1% sodium carrageenan (lambda carrageenan, Sigma Chemical Co., St Louis, MO) into the right hindpaw. Right paw volumes (ml) were measured immediately following injection of carrageenan for baseline volume measurements using a Buxco plethysmograph (Buxco Electronics, Inc., Troy, NY). Three hours after the injection of carrageenan, right paws were remeasured and paw edema calculated for each rat by subtracting the zero time reading from the 3 hour reading. Data are reported as mean percent inhibition +/- SEM. Statistical

significance of results was analyzed by Dunnetts multiple comparison test where $p < 0.05$ was considered statistically significant.

Rat Carrage nan Pleural Inflammation (CIP) Model

Pleural inflammation was induced in male adrenalectomized Sprague-Dawley rats following the method of Vinegar *et al.*, *Fed. Proc.* **1976**, *35*, 2447-2456. Animals were orally dosed with experimental compounds, 30 minutes prior to the intrapleural injection of 2% lambda carrageenan (Sigma Chemical Co., St. Louis MO). Four hours later the animals were euthanized and the pleural cavities lavaged with ice cold saline. The lavage fluid was then added to two volumes of ice cold methanol (final methanol concentration 66%) to lyse cells and precipitate protein. Eicosanoids were determined by EIA as described above.

The data illustrating the inhibition of prostaglandin biosynthesis *in vivo* by the compounds of this invention is shown in Table 3. Values reported are percent inhibition at 10 milligrams per kilogram body weight.

Carrageenan induced air pouch prostaglandin biosynthesis model (CAP)

Air pouches are formed in the backs of male Sprague Dawley rats by injecting 20 mL of sterile air on day 0. Three days later the pouch was reinflated with an additional 10 mL of sterile air. On day 7, 1 mL of saline containing 0.2 % lambda carrageenan (Sigma Chemical Co.) is injected into the pouch to induce the inflammatory reaction that is characterized by the release of prostaglandins. Test compounds are dosed at 0.1 to 10 mg/kg 30 minutes prior to carrageenan. Four hours after the carrageenan injection the pouch is lavaged and levels of prostaglandins are determined by enzyme immuno-assay using commercially available kits. Percent inhibitions are calculated by comparing the response in animals which have received vehicle to those which received compound. Values for Cox-2 inhibition that are parenthetical indicate ED_{50} values.

The data illustrating the inhibition of prostaglandin biosynthesis *in vivo* by the compounds of this invention is shown in Table 3. Values reported are percent inhibition at 10 milligrams per kilogram body weight for CIP and CPE tests and at 3 milligrams per kilogram body weight for CAP testing.

See attached table

Table 3

Example Numbers	CIP % Inhib. @ 10 mpk	CPE % Inhib. @ 10 mpk	CAP % Inhib. @ 3 mpk
10	44		
12	42	25	
34	36	31	
54	31	30	
58	42	14	67
62	57	21	
66	59	7	0
67	40 @ 3mpk		
68	64	40.3	
69	61	45.5 $ED_{30} = 5.4$	87
72			
73		46	29
74	46.5	18	34
77	51	21	
80	60	28.5	91
89	68.3 $ED_{50} = 3.4$	45.5	94
106			47
109		13	71
112		21	42.5
119	82	27	76
120	5	11	
121	19	8	
123			23
143			59
153			51

160	56	35	
166	40		59
168	0	6	
180	34.5		
182	59	27	98
185	59	20	53
187	51	28	30
190	60	28	71
205			54
226		21	40.5
243			7
245			47
246			48
248			49
256			47
257			60
261		28	79
330			4.5
335			45
339		43	90.5 $ED_{50} = 0.58$
346			49.5
347		27	66.5
349			63
351/64			0
352			89 $ED_{50} = 5.0$
353/63			0
361			65
366			63 $ED_{50} = 1.5$
367			48

375		47	91 $ED_{50} = 0.30$
376		17	77.5
378			59
384/33	51	15	51
385			65
388		28	80
390			60
391			61
392			60
394			70
395			71
396		23	85
397			70
400	65	41	95
403		43	68.5 $ED_{50} = 0.35$
405			53
406		23	66.5
407			61
419			48
427			78
445		15	73
446		44	92 $ED_{50} = 0.5$
449		23	76 $ED_{50} = 1.8$
450			86
451			80.5 $ED_{50} = 1$
452			71

Pharmaceutical Compositions

The present invention also provides pharmaceutical compositions which comprise compounds of the present invention formulated together with one or more non-toxic pharmaceutically acceptable carriers. The pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a compound of the present invention formulated together with one or more pharmaceutically acceptable carriers. As used herein, the term "pharmaceutically acceptable carrier" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the procedures and judgements well known to one skilled in the art. The pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, or as an oral or nasal spray.

The compounds of the present invention may be potentially useful in the treatment of several illness or disease states such as inflammatory diseases, dysmennorhea, asthma, premature labor, adhesions and in particular pelvic adhesions, osteoporosis, and ankylosing spondolitis. Current Drugs Ltd, ID Patent Fast Alert, AG16, May 9, 1997.

The compounds of the present invention may also be potentially useful in the treatment of cancers, and in particular, colon cancer. Proc. Natl. Acad. Sci., 94, pp. 3336-3340, 1997.

The compounds of the present invention may be useful by providing a pharmaceutical composition for inhibiting prostaglandin biosynthesis comprising a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt, ester, or prodrug thereof, and a pharmaceutrically acceptable carrier.

The compounds of the present invention may be useful by providing a pharmaceutical composition for inhibiting prostaglandin biosynthesis comprising a therapeutically effective amount of a compound of formula II or a pharmaceutically acceptable salt, ester, or prodrug thereof, and a pharmaceutrically acceptable carrier.

The compounds of the present invention may be useful by providing a pharmaceutical composition for inhibiting prostaglandin biosynthesis comprising a therapeutically effective amount of a compound of formula III or a pharmaceutically acceptable salt, ester, or prodrug thereof, and a pharmaceutrically acceptable carrier.

In addition, the compounds of the present invention may be useful by providing a method for inhibiting prostaglandin biosynthesis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt, ester, or prodrug thereof.

The compounds of the present invention may be useful by providing a method for inhibiting prostaglandin biosynthesis comprising administering to a mammal in need of such treatment a therapeutically effective amount a compound of formula II or a pharmaceutically acceptable salt, ester, or prodrug thereof.

The compounds of the present invention may be useful by providing a method for inhibiting prostaglandin biosynthesis comprising administering to a mammal in need of such treatment a therapeutically effective amount compound of formula III or a pharmaceutically acceptable salt, ester, or prodrug thereof.

In addition, the compounds of the present invention may be useful by providing a method for treating pain, fever, inflamation, rheumatoid arthritis, osteoarthritis, adhesions, and cancer comprising administering to a mammal in need of such teratment a therapeutically effective amount of a compound of formula I.

In addition, the compounds of the present invention may be useful by providing a method for treating pain, fever, inflamation, rheumatoid arthritis,

osteoarthritis, adhesions, and cancer comprising administering to a mammal in need of such teratment a therapeutically effective amount of a compound of formula II.

In addition, the compounds of the present invention may be useful by providing a method for treating pain, fever, inflamation, rheumatoid arthritis, osteoarthritis, adhesions, and cancer comprising administering to a mammal in need of such teratment a therapeutically effective amount of a compound of formula III.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (such as, for example, cottonseed, groundnut, corn, germ, olive, castor, sesame oils, and the like), glycerol, tetrahydrofurfuryl alcohol, poly-ethyl-ene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Injectable preparations, such as, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, such as, for example, a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, isotonic sodium chloride solution, and the like. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectable preparations.

The injectable formulations can be sterilized by any method known in the art, such as, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can

be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microencapsulated matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides) Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and thus melt in the rectum or vaginal cavity and release the active compound.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is usually mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as, for example, sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as, for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as, for example, glycerol, d) disintegrating agents such as, for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as, for example, paraffin, f) absorption accelerators such as, for example, quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as, for example, kaolin and bentonite clay, and) lubricants such

as, for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients such as, for example, lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using excipients such as, for example, lactose or milk sugar as well as high molecular weight polethylene glycols and the like.

The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulation art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as, for example, sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as, for example, magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients such as, for example, animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, poly-

ethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to the compounds of this invention, excipients such as, for example, lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in a suitable medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

According to the methods of treatment of the present invention, a patient, such as a human or mammal, is treated by administering to the patient a therapeutically effective amount of a compound of the invention, in such amounts and for such time as is necessary to achieve the desired result. By a "therapeutically effective amount" of a compound of the invention is meant a sufficient amount of the compound to provide the relief desired, at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

The total daily dose of the compounds of this invention administered to a human or other mammal in single or in divided doses can be in amounts, for example, from 0.001 to about 1000 mg/kg body weight daily or more preferably from about 0.1 to about 100 mg/kg body weight for oral administration or 0.01 to about 10 mg/kg for

parenteral administration daily. Single dose compositions may contain such amounts or submultiples thereof to make up the daily dose.

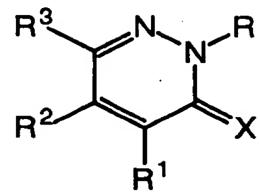
The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

The reagents required for the synthesis of the compounds of the invention are readily available from a number of commercial sources such as Aldrich Chemical Co. (Milwaukee, WI, USA); Sigma Chemical Co. (St. Louis, MO, USA); and Fluka Chemical Corp. (Ronkonkoma, NY, USA); Alfa Aesar (Ward Hill, MA 01835-9953); Eastman Chemical Company (Rochester, New York 14652-3512); Lancaster Synthesis Inc. (Windham, NH 03087-9977); Spectrum Chemical Manufacturing Corp. (Janssen Chemical) (New Brunswick, NJ 08901); Pfaltz and Bauer (Waterbury, CT. 06708). Compounds which are not commercially available can be prepared by employing known methods from the chemical literature.

CLAIMS

We Caim:

1. A compound of formula I:



I

where

X is selected from the group consisting of O, S, NR^4, $N\text{-}OR^a$, and $N\text{-}NR^bR^c$, wherein R^4 is selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, heterocyclic, heterocyclic alkyl, and arylalkyl; and R^a, R^b, and R^c are independently selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, aryl, and arylalkyl;

R is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkylcarbonylalkyl, alkylsulfonylalkyl, alkylsulfonylarylalkyl, alkoxy, alkoxyalkyl, carboxy, carboxyalkyl, cyanoalkyl, haloalkyl, haloalkenyl, haloalkynyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, arylhaloalkyl, arylhydroxyalkyl, aryloxy, aryloxyhydroxyalkyl, aryloxyhaloalkyl, arylcarbonylalkyl, haloalkoxyhydroxyalkyl, heterocyclic, heterocyclic alkyl, heterocyclic alkoxy, heterocyclic oxy, $-C(O)R^5$, $-(CH_2)_nC(O)R^5$, $-R^6\text{-}R^7$, $-(CH_2)_nCH(OH)R^5$, $-(CH_2)_nCH(OR^d)R^5$, $-(CH_2)_nC(NOR^d)R^5$, $-(CH_2)_nC(NR^d)R^5$, $-(CH_2)_nCH(NOR^d)R^5$, $-(CH_2)_nCH(NR^dR^e)R^5$, $-(CH_2)_nC\equiv C\text{-}R^7$, $-(CH_2)_n[CH(CX'_3)]_m\text{-}(CH_2)_n\text{-}CX'_3$, $-(CH_2)_n(CX'_2)_m\text{-}(CH_2)_n\text{-}CX'_3$, $-(CH_2)_n[CH(CX'_3)]_m\text{-}(CH_2)_n\text{-}R^8$, $-(CH_2)_n(CX'_2)_m\text{-}(CH_2)_n R^8$, $-(CH_2)_n(CHX')_m\text{-}(CH_2)_n\text{-}CX'_3$, $-(CH_2)_n(CHX')_m\text{-}(CH_2)_n\text{-}R^8$, and $-(CH_2)_n\text{-}R^{20}$,

wherein R^5 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, haloalkenyl, haloalkynyl, heterocyclic, and heterocyclic alkyl;

wherein R^6 is alkylene or alkenylene, or halo-substituted alkylene halo-substituted alkenylene;

R^7 and R^8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclic, and heterocyclic alkyl;

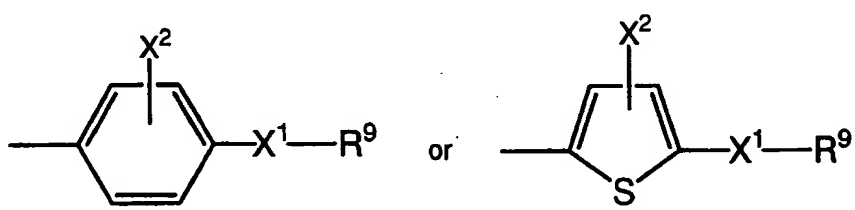
R^{20} is selected from the group consisting of alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkenyl, aryl, heterocyclic, and heterocyclic alkyl;

R^d and R^e are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclic, and heterocyclic alkyl;

X' is halogen;

n is from 0 to about 10, and m is 0 to about 5;

at least one of R^1, R^2 and R^3 is



where X^1 is selected from the group consisting of $-SO_2-$, $-SO(NR^{10})-$, -SO-, $-SeO_2-$, $PO(OR^{11})-$, and $-PO(NR^{12}R^{13})-$,

R^9 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, amino, $-NHNH_2$, $-N{=}CH(NR^{10}R^{11})$, dialkylamino, alkoxy, thiol, alkylthiol, protecting groups, and protecting groups attached to X^1 by an alkylene;

X^2 is selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, and alkynyl;

R^{10}, R^{11}, R^{12}, and R^{13} are independently selected from the group consisting of hydrogen, alkyl, and cycloalkyl, or R^{12} and R^{13} can be taken together, with the nitrogen to which they are attached, to form a heterocyclic ring having from 3 to 6 atoms.

The remaining two of the groups of R^1, R^2, and R^3, are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, halogen, alkyl, alkenyl, alkynyl, alkylamino, alkenyloxy, alkylthio,

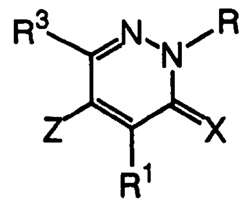
alkylthioalkoxy, alkoxy, alkoxyalkyl, alkoxyalkylamino, alkoxyalkoxy, amido, amidoalkyl, haloalkyl, haloalkenyloxy, haloalkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkenylalkoxy, cycloalkylalkoxy, cycloalkylalkylamino, cycloalkylamino, cycloalkyloxy, cycloalkylidenealkyl, amino, aminocarbonyl, aminoalkoxy, aminocarbonylalkyl, alkylaminoaryloxy, dialkylamino, dialkylaminoaryloxy, arylamino, arylalkylamino, diarylamino, aryl, arylalkyl, arylalkylthio, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, heterocyclic, heterocyclic alkyl, heterocyclic(alkyl) amino, heterocyclic alkoxy, heterocyclic amino, heterocyclic oxy, heterocyclic thio, hydroxy, hydroxyalkyl, hydroxyalkylamino, hydroxyalkoxy,hydroxyalkylthio, mercaptoalkoxy, oxoalkoxy, cyano, nitro, and -Y-R^{14}, wherein Y is selected from the group consisting of -O-, -S-, -C(R^{16}) (R^{17})-, -C(O)N$R^{21}R^{22}$-, -C(O)-, -C(O)O-, -NH-, -NC(O)-, -N=C $R^{21}R^{22}$, N- $R^{21}R^{22}$, and -NR^{19}-. R^{14} is selected from the group consisting of hydrogen, halogen, alkyl, alkoxyalkyl, alkylthioalkyl, alkenyl, alkynyl, hydroxy, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, cycloalkenyl, amino, cyano, aryl, arylalkyl, heterocyclic, and heterocyclic(alkyl),

R^{16}, R^{17}, and R^{19} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano; and

R^{21} and R^{22} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano;

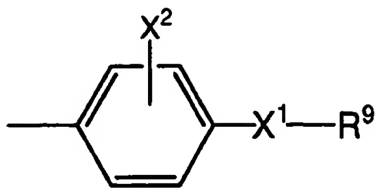
or a pharmaceutically acceptable salt, ester, or prodrug thereof.

2. A compound having the formula <u>II</u>:

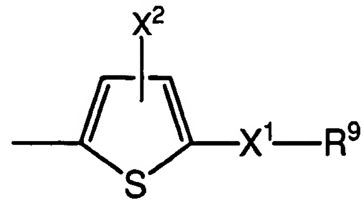


II

wherein Z is a group having the formula:



or



where X^1 is selected from the group consisting of $-SO_2-$, -SO-, $-SeO_2-$,$SO(NR^{10})-$, and R^9 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, amino, $-NHNH_2$, dialkylamino, alkoxy, thiol, alkylthiol, protecting groups, and protecting groups attached to X^1 by an alkylene;

R^{10} is selected from the group consisting of hydrogen, alkyl, and cycloalkyl;

X^2 is selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, and alkynyl;

R is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkylcarbonylalkyl, alkylsulfonylalkyl, alkylsulfonylarylalkyl, alkoxy, alkoxyalkyl, carboxy, carboxyalkyl, cyanoalkyl, haloalkyl, haloalkenyl, haloalkynyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, arylhaloalkyl, arylhydroxyalkyl, aryloxy, aryloxyhydroxyalkyl, aryloxyhaloalkyl, arylcarbonylalkyl, haloalkoxyhydroxyalkyl, heterocyclic, heterocyclic alkyl, heterocyclic alkoxy, heterocyclic oxy, $-C(O)R^5$, $-(CH_2)_nC(O)R^5$, $-R^6-R^7$, $-(CH_2)_nCH(OH)R^5$, $-(CH_2)_nCH(OR^d)R^5$, $-(CH_2)_nC(NOR^d)R^5$, $-(CH_2)_nC(NR^d)R^5$, $-(CH_2)_nCH(NOR^d)R^5$, $-(CH_2)_nCH(NR^dR^e)R^5$, $-(CH_2)_nC{\equiv}C-R^7$, $-(CH_2)_n[CH(CX'_3)]_m-(CH_2)_n-CX'_3$, $-(CH_2)_n(CX'_2)_m-(CH_2)_n-CX'_3$, $-(CH_2)_n[CH(CX'_3)]_m-(CH_2)_n-R^8$, $-(CH_2)_n(CX'_2)_m-(CH_2)_n R^8$, $-(CH_2)_n(CHX')_m-(CH_2)_n-CX'_3$, $-(CH_2)_n(CHX')_m-(CH_2)_n-R^8$, and $-(CH_2)_n-R^{20}$,

wherein R^5 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, haloalkenyl, haloalkynyl, heterocyclic, and heterocyclic alkyl;

wherein R^6 is alkylene or alkenylene, or halo-substituted alkylene halo-substituted alkenylene;

R^7 and R^8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclic, and heterocyclic alkyl;

R^{20} is selected from the group consisting of alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkenyl, aryl, heterocyclic, and heterocyclic alkyl;

R^d and R^e are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclic, and heterocyclic alkyl;

X' is halogen;

n is from 0 to about 10, and m is 0 to about 5;

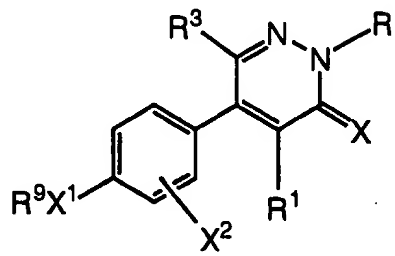
R^1, and R^3 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, halogen, alkyl, alkenyl, alkynyl, alkylamino, alkenyloxy, alkylthio, alkylthioalkoxy, alkoxy, alkoxyalkyl, alkoxyalkylamino, alkoxyalkoxy, amido, amidoalkyl, haloalkyl, halolkenyloxy, haloalkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkenylalkoxy, cycloalkylalkoxy, cycloalkylalkylamino, cycloalkylamino, cycloalkyloxy, amino, aminocarbonyl, aminoalkoxy, aminocarbonylalkyl, alkylaminoaryloxy, dialkylamino, dialkylaminoaryloxy, arylamino, arylalkylamino, diarylamino, aryl, arylalkyl, arylalkylthio, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, heterocyclic, heterocyclic alkyl, heterocyclic(alkyl) amino, heterocyclic alkoxy, heterocyclic amino, heterocyclic oxy, heterocyclic thio, hydroxy, hydroxyalkyl, hydroxyalkylamino, hydroxyalkoxy, mercaptoalkoxy, oxoalkoxy, cyano, nitro, and -Y-R^{14}, wherein Y is selected from the group consisting of -O-, -S-, -C(R^{16})(R^{17})-, -C(O)N$R^{21}R^{22}$-, -C(O)-, -C(O)O-, -NH-, -NC(O)-, -N=C $R^{21}R^{22}$, N-$R^{21}R^{22}$, and -NR^{19}-. R^{14} is selected from the group consisting of hydrogen, halogen, alkyl, alkoxyalkyl, alkylthioalkyl, alkenyl, alkynyl, hydroxy, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, cycloalkenyl, amino, cyano, aryl, arylalkyl, heterocyclic, and heterocyclic(alkyl),

R^{16}, R^{17}, and R^{19} are independently selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano; and

R^{21} and R^{22} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

3. A compound having the formula **III**:



III

wherein X, X^1, X^2, R, R^1, R^3, and R^9 are as defined in claim 1; or a pharmaceutically acceptable salt, ester, or prodrug thereof.

4. A compound of claim 3 wherein X^1 is selected from the group consisting of $-SO_2-$, $-SO-$, $-SeO_2-$, and $-SO(NR^{10})-$, and R^9 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, amino, alkylamino, or dialkylamino;

X^2 is selected from the group consisting of hydrogen and halogen;

X is selected from the group consisting of O, S, NR^4, $N\text{-}OR^a$, and $N\text{-}NR^bR^c$, wherein R^4 is selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, heterocyclic, heterocyclic alkyl, and arylalkyl; and R^a, R^b, and R^c.are independently selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, aryl, and arylalkyl;

R is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkylcarbonylalkyl, alkylsulfonylalkyl, alkylsulfonylarylalkyl, carboxyalkyl, cyanoalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkenyl, arylalkynyl, heterocyclic, heterocyclic alkyl, arylalkyl, $-(CH_2)_nC(O)R^5$, $-(CH_2)_nC{\equiv}C\text{-}R^7$, $-(CH_2)_n[CH(CX'_3)]_m(CH_2)_n\text{-}R^8$, and $-(CH_2)_n\text{-}R^{20}$;

wherein R^5 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, heterocyclic, and heterocyclic alkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, heterocyclic, and heterocyclic alkyl,

R^{20} is selected from the group consisting of alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkenyl, aryl, heterocyclic, and heterocyclic alkyl;

X' is halogen;

n is from 0 to about 10, m is from 0 to about 5;

$R^1$and R^3 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, halogen, alkyl, alkenyl, alkynyl, alkoxy, alkenyloxy, alkoxyalkyl, amido, amidoalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, amino, aminocarbonyl, aminocarbonylalkyl, alkylamino, dialkylamino, arylamino, arylalkylamino, diarylamino, aryl, aryloxy, heterocyclic, heterocyclic alkyl, cyano, nitro, and -Y-R^{14}, wherein Y is selected from the group consisting of, -O-, -S-, -C(R^{16}) (R^{17})-, -C(O)N$R^{21}R^{22}$-, -C(O)-, -C(O)O-, -NH-, -NC(O)-, -N=C $R^{21}R^{22}$, N- $R^{21}R^{22}$, and -NR^{19}-. R^{14} is selected from the group consisting of hydrogen, halogen, alkyl, alkoxyalkyl, alkylthioalkyl, alkenyl, alkynyl, hydroxy, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, cycloalkenyl, amino, cyano, aryl, arylalkyl, heterocyclic, and heterocyclic(alkyl),

R^{16}, R^{17}, and R^{19} are independently selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano; and

R^{21} and R^{22} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

5. A compound of claim 3 wherein X^1 is selected from the group consisting of -SO_2-, -SO-, -SeO_2-, and -SO(NR^{10})-, and R^9 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, amino, alkylamino, or dialkylamino;

X^2 is selected from the group consisting of hydrogen and halogen;

X is selected from the group consisting of O, S, NR^4, N-OR^a, and N-NR^bR^c, wherein R^4 is selected from the group consisting of alkyl, alkenyl, cyclo-

alkyl, cycloalkenyl, cycloalkylalkyl, alkylcycloalkenyl, aryl, heterocyclic, and arylalkyl; and R^a, R^b, and R^c.are independently selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, aryl, and arylalkyl;

R is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkylcarbonylalkyl, alkylsulfonylalkyl, alkylsulfonylarylalkyl, carboxyalkyl, cyanoalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkenyl, arylalkynyl, heterocyclic, heterocyclic alkyl, arylalkyl, $-(CH_2)_nC(O)R^5$, and -$(CH_2)n$-R^{20};

wherein R^5 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, heterocyclic, and heterocyclic alkyl;

R^{20} is selected from the group consisting of alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkenyl, aryl, heterocyclic, and heterocyclic alkyl;

n is from 0 to about 10;

$R^1$and R^3 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, halogen, alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, alkylthioalkyl, aryloxyalkyl, arylthioalkyl, amido, amidoalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, amino, aminocarbonyl, aminocarbonylalkyl, alkylamino, alkylaminoalkyl, dialkylamino, arylamino, arylalkylamino, diarylamino, aryl, heterocyclic, heterocyclic(alkyl), cyano, nitro, and -Y-R^{14}, wherein Y is selected from the group consisting of, -O-, -S-, -C(R^{16}) (R^{17})-, -C(O)N$R^{21}R^{22}$-, -C(O)-, -C(O)O-, -NH-, -NC(O)-, and -NR^{19}-. R^{14} is selected from the group consisting of hydrogen, halogen, alkyl, alkoxyalkyl, alkylthioalkyl, alkenyl, alkynyl, hydroxy, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, cycloalkenyl, amino, cyano, aryl, arylalkyl, heterocyclic, and heterocyclic(alkyl), and

R^{16}, R^{17}, and R^{19} are independently selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano;

R^{21} and R^{22} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

6. A compound of claim 3 wherein X^1 is selected from the group consisting of $-SO_2-$, -SO-, $-SeO_2-$, and-SO(NR^{10})-, and R^9 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, amino, alkylamino, or dialkylamino;

X^2 is selected from the group consisting of hydrogen and halogen;

X is selected from the group consisting of O, S, NR^4, N-OR^a, and N-NR^bR^c, wherein R^4 is selected from the group consisting of alkyl, alkenyl, cyclo-alkyl, cycloalkenyl, cycloalkylalkyl, alkylcycloalkenyl, aryl, heterocyclic, and arylalkyl; and R^a, R^b, and R^c.are independently selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, aryl, and arylalkyl;

R is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkylcarbonylalkyl, alkylsulfonylalkyl, alkylsulfonylarylalkyl, carboxyalkyl, cyanoalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkenyl, arylalkynyl, heterocyclic, heterocyclic alkyl, arylalkyl, and $-(CH_2)_nC(O)R^5$,;

wherein R^5 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, heterocyclic, and heterocyclic alkyl; and

n is from 0 to about 10;

$R^1$and R^3 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, halogen, alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, alkylthioalkyl, aryloxyalkyl, arylthioalkyl, amido, amidoalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, amino, aminocarbonyl, aminocarbonylalkyl, alkylamino, alkylaminoalkyl, dialkylamino, arylamino, arylalkylamino, diarylamino, aryl, heterocyclic, heterocyclic(alkyl), cyano, nitro, and -Y-R^{14}, wherein Y is selected from the group consisting of, -O-, -S-, -C(R^{16}) (R^{17})-, -C(O)$NR^{21}R^{22}$-, -C(O)-, -C(O)O-, -NH-, -NC(O)-, and -NR^{19}-. R^{14} is selected from the group consisting of hydrogen, halogen, alkyl, alkoxyalkyl, alkylthioalkyl, alkenyl, alkynyl, hydroxy, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, cycloalkenyl, amino, cyano, aryl, arylalkyl, heterocyclic, and heterocyclic(alkyl);

R^{15}, R^{16}, R^{17}, and R^{19} are independently selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl or cyano;

R^{21} and R^{22} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

7. A compound of claim 3 wherein X^1 is selected from the group consisting of $-SO_2-$, $-SO-$, $-SeO_2-$, and $-SO(NR^{10})-$, and R^9 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, amino, alkylamino, or dialkylamino;

X^2 is selected from the group consisting of hydrogen and halogen;

X is selected from the group consisting of O, S, NR^4, $N\text{-}OR^a$, and $N\text{-}NR^bR^c$, wherein R^4 is selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, alkylcycloalkenyl, aryl, heterocyclic, and arylalkyl; and R^a, R^b, and R^c.are independently selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, aryl, and arylalkyl;

R is selected from alkyl, haloalkyl, aryl, heterocyclic, heterocyclic alkyl, and $-(CH_2)n-R^{20}$ where is R^{20} is substituted and unsubstituted aryl wherein the substituted aryl compounds are substituted with halogen;

n is from 0 to about 10;

R^1 is selected from the group consisting of alkoxy, alkenyloxy, hydroxyalkoxy, aryloxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, and $-Y-R^{14}$, wherein Y is selected from the group consisting of, -O-, -S-, $-C(R^{16})(R^{17})-$, -C(O)-, -C(O)O-, -NH-, -NC(O)-, and $-NR^{19}-$. R^{14} is selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkynyl, hydroxy, cycloalkyl, cycloalkenyl, amino, cyano, aryl, arylalkyl, heterocyclic, and heterocyclic alkyl,

R^3 is hydrogen;

R^{15}, R^{16}, R^{17}, and R^{19} are independently selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano; and

R^{21} and R^{22} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

8. A compound of claim 3 wherein X^1 is selected from the group consisting of $-SO_2-$, -SO-, and $-SO(NR^{10})-$, and R^9 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, amino, alkylamino, or dialkylamino;

X^2 is selected from the group consisting of hydrogen and halogen;

X is selected from the group consisting of O, S, NR^4, $N\text{-}OR^a$, and $N\text{-}NR^bR^c$, wherein R^4 is selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, alkylcycloalkenyl, aryl, heterocyclic, and arylalkyl; and R^a, R^b, and R^c.are independently selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, aryl, and arylalkyl;

R is selected from alkyl, haloalkyl, aryl, heterocyclic, heterocyclic alkyl, and $-(CH_2)n-R^{20}$ where is R^{20} is substituted and unsubstituted aryl wherein the substituted aryl compounds are substituted with halogen;

n is from 0 to about 10;

R^1 is selected from the group consisting of alkoxy, alkenyloxy, hydroxyalkoxy, aryloxy, aryl, arylalkyl, heterocyclic, and heterocyclic alkyl; and

R^3 is hydrogen;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

9. A compound of claim 3 wherein X^1 is $-SO_2-$ and and R^9 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, amino, alkylamino, or dialkylamino;

X^2 is selected from the group consisting of hydrogen and halogen;

X is selected from the group consisting of O, S, NR^4, $N\text{-}OR^a$, and $N\text{-}NR^bR^c$, wherein R^4 is selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, alkylcycloalkenyl, aryl, heterocyclic, and arylalkyl; and R^a, R^b, and R^c.are independently selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, aryl, and arylalkyl;

R is selected from haloalkyl, aryl, heterocyclic, heterocyclic alkyl, and $-(CH_2)n-R^{20}$ where is R^{20} is substituted and unsubstituted aryl wherein the substituted aryl compounds are substituted with halogen;

n is from 0 to about 10;

R^1 is selected from the group consisting of unsubstituted aryl, and substituted aryl with one, two, or three substituents selected from the group consisting of fluorine and chlorine including, but not limited to, *p*-chlorophenyl, *p*-fluorophenyl, 3,4-dichlorophenyl, 3-chloro-4-fluoro-phenyl, and the like; and

R^3 is hydrogen;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

10. A compound of claim 3 wherein X^1 is $-SO_2-$,and R^9 is selected from the group consisting of alkyl and amino;

X^2 is selected from the group consisting of hydrogen and halogen;

X is O;

R is selected from the group consisting of alkyl, alkenyl, alkynyl, haloalkyl, aryl, and arylalkyl;

R^1 is selected from the group consisting of alkoxy, aryl, alkenyloxy, hydroxyalkoxy, haloalkoxy, arylalkyl, alkyl, and aryloxy; and

R^3 is hydrogen;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

11. A compound of claim 3 wherein X^1 is $-SO_2-$, and R^9 is selected from the group consisting of alkyl and amino;

X^2 is selected from hydrogen and fluorine;

R is selected from haloalkyl, aryl, and alkyl;

n is from 0 to about 10;

R^1 is selected from the group consisting of isobutyloxy, isopentyloxy, 1-(3-methyl-3-butenyl)oxy, 2-hydroxy-2-methyl-propyloxy, 3-hydroxy-3-methyl-butyloxy, neopentyloxy, isopentyl, aryloxy including 4-fluorophenoxy, unsubstituted

aryl, and substitued aryl with one, two, or three substituents selected from the group consisting of fluorine and chlorine including, , 4-fluorophenyl, 4-chlorophenyl, 3-chloro-4-fluoro-phenyl4-chloro-3-fluoro-phenyl; and

R^3 is hydrogen;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

12. A compound of claim 3 wherein X^1 is selected from the group consisting of $-SO_2-$, and $-SO(NR^{10})-$, and R^9 is alkyl,

X^2 is selected from the group consisting of hydrogen and fluorine;

X is O;

R is selected from the group consisting of alkyl, alkenyl, alkynyl, haloalkyl, aryl, and arylalkyl;

R^1 is selected from the group consisting of alkoxy, aryl, alkenyloxy, hydroxyalkoxy, alkyl, and aryloxy; and

R^3 is hydrogen;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

13. A compound of claim 3 wherein X^1 is $-SO_2-$, R^9 is amino;

X^2 is selected from the group consisting of hydrogen and fluorine;

X is O;

R is selected from the group consisting of alkyl, alkenyl, alkynyl, haloalkyl, aryl, and arylalkyl;

R^1 is selected from the group consisting of alkoxy, aryl, alkenyloxy, hydroxyalkoxy, alkyl, and aryloxy; and

R^3 is hydrogen;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

14. A compound of claim 3 wherein X^1 is $-SO_2-$, and R^9 is methyl;

X^2 is selected from the group consisting of hydrogen;

X is O;

R is selected from the group consisting t-butyl, 3-chlorophenyl, 3,4-difluorophenyl, 4-fluorophenyl, 4-chloro-3-fluoro-phenyl, 3-chloro-4-fluoro-phenyl, and CF_3CH_2-, ;

R^1 is selected from the group consisting of aryloxy, isobutyloxy, isopentyloxy, 1-(3-methyl-3-butenyl)oxy, 2-hydroxy-2-methyl-propyloxy, 3-hydroxy-3-methyl-butyloxy, neopentyloxy, isopentyl, 4-fluorophenyl, 4-chlorophenyl, 4-chloro-3-fluoro-phenyl,4-fluorophenoxy; and

R^3 is hydrogen;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

15. A compound of claim 3 wherein X^1 is $-SO_2-$, and R^9 is amino;

X^2 is selected from the group consisting of hydrogen;

X is O;

R is selected from the group consisting t-butyl, 3-chlorophenyl, 3,4-difluorophenyl, 4-fluorophenyl, 4-chloro-3-fluoro-phenyl, 3-chloro-4-fluoro-phenyl and CF_3CH_2-, ;

R^1 is selected from the group consisting of aryloxy, isobutyloxy, isopentyloxy, 1-(3-methyl-3-butenyl)oxy, 2-hydroxy-2-methyl-propyloxy, 3-hydroxy-3-methyl-butyloxy, neopentyloxy, isopentyl, 4-fluorophenyl, 4-chlorophenyl, 4-chloro-3-fluoro-phenyl,4-fluorophenoxy; and

R^3 is hydrogen;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

16. A compound according to claim 3, selected from the group consisting of:

2-(2,2,2-Trifluoroethyl)-4-(4-chlorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(3-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3-Chlorophenyl)-4-(3-methyl-3-butenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(2,2,2-Trifluoroethyl)-4-(4-chloro-3-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-fluorophenyl)-4-(4-flurophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(3-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(*t*-Butyl)-4-(3-methylbutoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(*t*-Butyl)-4-(3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(2,2,2-Trifluoroethyl)-4-(2,2-dimethylpropoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(2,2,2-Trifluoroethyl)-4-(2-methylpropoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(3-methylbutoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(3-methylbutyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3-Chlorophenyl)-4-(3-methylbutoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3-Chlorophenyl)-4-(3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(2-methylpropoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3-Chlorophenyl)-4-(2-methylpropoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(3-methylbutoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(2-methylpropoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(2-methylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(2-methylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(4-fluorophenoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;
2-(4-Fluorophenyl)-4-(4-fluorophenoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(2,2,2-Trifluoroethyl)-4-(2,2-dimethylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Chloro-3-fluorophenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(4-fluorophenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)- -4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]- 3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2,4-Bis(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-3(2H)-pyridazinone;

2-(4-fluorophenyl)-4-(4-flurophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone; and

2-(3,4-Difluorophenyl)-4-(2-hydroxy-2-methylpropoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(2-oxopropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(2-methoxy-imino-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

(R)-2-(3,4-Difluorophenyl)-4-(3-hydroxy-2-methylpropoxy)-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone;

(S)- 2-(3,4-Difluorophenyl)-4-(3-hydroxy-2-methylpropoxy)-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone;

(R)-2-(3,4-Difluorophenyl)-4-(3-hydroxy-2-methylpropoxy)-5-[4-(aminosulfonyl)-phenyl]-3(2H)-pyridazinone;

(S)- 2-(3,4-Difluorophenyl)-4-(3-hydroxy-2-methylpropoxy)-5-[4-(aminosulfonyl)-phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(3-oxo-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(3-oxo-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone; and

2,4-Bis(4-Flurophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

17. A compound of claim 16 selected from the group consisting of

2-Phenyl-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-3(2H)-pyridazinone;
2-(2,2,2-Trifluoroethyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-3(2H)-pyridazinone;

2-(2,2,2-Trifluoroethyl)-4-(4-chlorophenyl)-5-(4-methylsulfonylphenyl)-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(2-methylpropoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone; and

2,4-Bis(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-3(2H)-pyridazinone;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

18. A pharmaceutical composition for inhibiting prostaglandin biosynthesis comprising a therapeutically effective amount of the compound of claim 1 and a pharmaceutrically acceptable carrier.

19. A pharmaceutical composition for inhibiting prostaglandin biosynthesis comprising a therapeutically effective amount of the compound of claim 2 and a pharmaceutrically acceptable carrier.

20. A pharmaceutical composition for inhibiting prostaglandin biosynthesis comprising a therapeutically effective amount of the compound of claim 3 and a pharmaceutrically acceptable carrier.

21. A method for inhibiting prostaglandin biosynthesis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of claim 1.

22. A method for inhibiting prostaglandin biosynthesis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of claim 2.

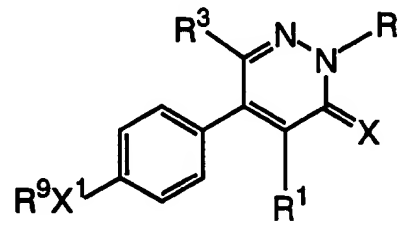
23. A method for inhibiting prostaglandin biosynthesis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of claim 3.

24. A method for treating pain, fever, inflamation, rheumatoid arthritis, osteoarthritis, adhesions, and cancer comprising administering to a therapeutically effective amount of a compound of claim 1.

25. A method for treating pain, fever, inflamation, rheumatoid arthritis, osteoarthritis, adhesions, and cancer comprising administering to a therapeutically effective amount of a compound of claim 2.

26. A method for treating pain, fever, inflamation, rheumatoid arthritis, osteoarthritis, adhesions, and cancer comprising administering to a therapeutically effective amount of a compound of claim 3.

27. A method for the preparation of a compound of claim 3 , or a pharmaceutically acceptable salt, ester, or prodrug thereof having the formula :



III

wherein X, X^1, X^2, R, R^1, R^3, and R^9 are as defined in claim 1;

comprising the step of reacting a compound having formula III, where R is hydrogen, with an alkylating agent.

28. The method according to claim 27 wherein the alkylating agent has the formula R^{99}-Q where Q is a leaving group and R^{99} is selected from the group consisting of methyl, ethyl, 1,1,1-trifluoroethyl, cyclopropylmethyl, 3-(2-methyl)-propenyl, 4-(2-methyl)but-2-enyl, 1,1-dichloropropen-3-yl, 2,2-dimethyl-3-oxo-4-butyl, 2,3,3,4,4,4-hexafluoro-n-buten-1-yl, propargyl, phenylpropargyl, phenyl, phenethyl, 1-phenylpropen-3-yl, benzyl, α-methyl-4-fluorobenzyl, 2,3,4,5,6-pentafluorobenzyl, 4-trifluomethoxyphenacyl, 4-fluorobenzyl, 4-fluoro-phenyl, 2-trifluoromethylbenzyl, 2,4-difluorobenzyl, 2,4-difluorophenacyl, 4-trifluomethylphenacyl, phenacyl, 4-carboxyphenacyl, 4-chlorophenacyl, 4-cyanophenacyl, 4-diethylaminophenacyl, 3-thienylmethyl, 5-methylthien-2-ylmethyl, 5-chlorothien-2-ylmethyl, 2-benzo[b]thienylmethyl, 3-benzothienacyl, 5-chlorothiazol-2-ylmethyl, 5-methylthiazol-2-ylmethyl, 2-pyridylmethyl, 3-pyridyl-methyl, 4-pyridylmethyl, quinolin-2-ylmethyl, and fluoroquinolin-2-ylmethyl.

29. The method according to claim 27 wherein the alkylating agent has the formula R^{99}-Q where Q is a leaving group and R^{99} is selected from the group consisting of methyl, ethyl, 1,1,1-trifluoroethyl, cyclopropylmethyl, 3-(2-methyl)-propenyl, 4-(2-methyl)but-2-enyl, 1,1-dichloropropen-3-yl, 2,3,3,4,4,4-hexafluoro-n-buten-1-yl, propargyl, phenylpropargyl, phenyl, phenethyl, 1-phenylpropen-3-yl, benzyl, α-methyl-4-fluorobenzyl, 2,3,4,5,6-pentafluorobenzyl, 4-trifluomethoxy-phenacyl, 4-fluorobenzyl, 4-fluorophenyl, 2,4-difluorobenzyl, 2,4-difluorophenacyl, 4-trifluomethylphenacyl, phenacyl, 4-carboxyphenacyl, 4-chlorophenacyl, 4-cyanophenacyl, 4-diethylaminophenacyl, 3-thienylmethyl, 5-methylthien-2-yl-methyl, 5-chlorothien-2-ylmethyl, 2-benzo[b]thienylmethyl, and 3-benzothienacyl.

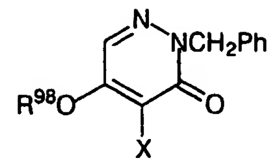
30. The method according to claim 27 wherein the alkylating agent has the formula R^{99}-Q where Q is a leaving group and R^{99} is selected from the group consisting of 1,1,1-trifluoroethyl, 3-(2-methyl)propenyl, 4-(2-methyl)but-2-enyl, 1,1-dichloropropen-3-yl, 2,3,3,4,4,4-hexafluoro-n-buten-1-yl, propargyl, phenyl-propargyl, phenyl, benzyl, α-methyl-4-fluorobenzyl, 2,3,4,5,6-pentafluorobenzyl, 4-fluorobenzyl, 4-fluorophenyl, 2,4-difluorobenzyl, 3-thienylmethyl, 5-methylthien-2-ylmethyl, 5-chlorothien-2-ylmethyl, and 2-benzo[b]thienylmethyl.

31. The method according to claim 27 wherein the alkylating agent has the formula R^{99}-Q where Q is a leaving group and R^{99} is selected from the group consisting of 1,1,1-trifluoroethyl, phenyl, benzyl, α-methyl-4-fluorobenzyl, 4-fluoro-benzyl, 4-fluorophenyl, and 2,4-difluorobenzyl.

32. The method according to claim 27 wherein the alkylating agent has the formula R^{99}-Q where Q is a leaving group and R^{99} is selected from the group consisting of 1,1,1-trifluoroethyl, benzyl, and 4-fluorophenyl.

33. A method for regioselectively preparing a 4,5- substituted pyridazone comprising the steps of

a) reacting a compound with the formula



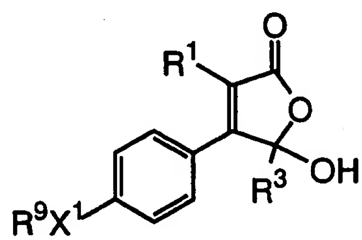
where R is an alkyl or aryl group, and X is a leaving group with a nucleophilic agent to displace the X group;

b) converting the $-OR^{98}$ to a leaving group; and

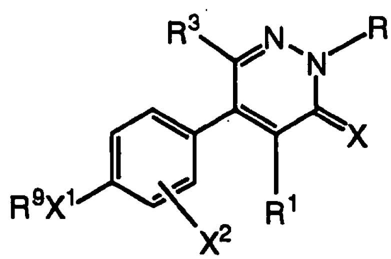
c) reacting the compound with a second nucleophilic agent to provide the 4,5- substituted pyridazone.

34. The method according to claim 33 wherein the benzyl group is removed using a Lewis acid.

35. A method for regioselectivly preparing a 4,5- substituted pyridazone comprising the steps of treating a compound having the formula



with a hydrazine having the formula $RNHNH_2$ to furnish the pyridazone having the formula:



III

wherein X, X^1, X^2, R, R^1, R^3, and R^9 are as defined in claim 1; or a pharmaceutically acceptable salt, ester, or prodrug thereof.

INTERNATIONAL SEARCH REPORT

Intern .al Application No
PCT/US 98/16479

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D237/14 C07D401/06 C07D403/06 C07D237/18 C07D409/06
C07D413/06 C07D405/06 A61K31/50 C07F11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 714 895 A (F. HOFFMANN-LA ROCHE AG) 5 June 1996 see claims 1-23 ---	1-35
A	EP 0 711 759 A (ROHM AND HAAS COMPANY) 15 May 1996 see claims 1-8 ---	1-35
A	WO 88 09675 A (MEDICIS CORPORATION) 15 December 1988 see claims 3,4 ---	1-35

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 October 1998	15/10/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Herz, C

1

Interr. ıal Application No
PCT/US 98/16479

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	D. E. GRISWOLD, J. L. ADAMS: "Constitutive Cyclooxygenase (COX-1) and Inducible Cyclooxygenase (COX-2): Rationale for Selective Inhibition and Progress to Date" MEDICINAL RESEARCH REVIEWS, vol. 16, no. 2, 1996, pages 181-206, XP002040558 -----	1-35

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. al Application No
PCT/US 98/16479

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 714895 A	05-06-1996	US 5622948 A	22-04-1997
		AU 3906295 A	06-06-1996
		BR 9505610 A	16-09-1997
		CA 2163490 A	02-06-1996
		CN 1132206 A	02-10-1996
		CZ 9503169 A	12-06-1996
		FI 955783 A	02-06-1996
		HU 75117 A	28-04-1997
		JP 8208639 A	13-08-1996
		NO 954878 A	03-06-1996
		PL 311536 A	10-06-1996
		SG 33609 A	18-10-1996
		ZA 9510027 A	03-06-1996
EP 711759 A	15-05-1996	AU 691673 B	21-05-1998
		AU 3666695 A	23-05-1996
		BR 9505160 A	21-10-1997
		CA 2162775 A	15-05-1996
		CN 1128758 A	14-08-1996
		CZ 9502989 A	15-05-1996
		HU 72912 A	28-06-1996
		JP 8225540 A	03-09-1996
		NZ 280413 A	26-07-1996
		PL 311361 A	27-05-1996
		ZA 9509612 A	29-05-1996
WO 8809675 A	15-12-1988	NONE	

374	2 @ 100	(0.02)
375	46 @ 100 31 @ 10	(0.18)
376	12 @ 100	(0.027)
381	0 @ 100	(0.188)
384	82 @ 100 49 @ 10	99 @ 1 78 @ 0.1
386	58 @ 100 47 @ 1	83 @ 1 63 @ 0.1 58 @ 0.01
387	57 @ 10 60 @ 1	76 @ 1 65 @ 0.1 56 @ 0.01
388	74 @ 10 36 @ 1	(0.049)
390	88 @ 10 45 @ 1	99 @ 10 72 @ 1 60 @ 0.1
392	56 @ 100 35 @ 10	82 @ 0.1 65 @ 0.01
393	15 @ 100	85 @ 1 58 @ 0.1
394	86 @ 100 38 @ 10	94 @ 1 64 @ 0.1 20 @ 0.01

395	91 @ 100 35 @ 10	93 @ 1 77 @ 0.1 34 @ 0.01
396	22 @ 100	(0.059)
397	25 @ 100	93 @ 1 58 @ 0.1 39 @ 0.01
398	26 @ 100	(0.202)
400	27 @ 100	(0.142)
401	(0.753)	96 @ 1 62 @ 0.1 48 @ 0.01
402	89 @ 1	(0.221)
403	(150.76)	92 @ 1 64 @ 0.1 36 @ 0.01
404	77 @ 100 47 @ 10	92 @ 0.1 57 @ 0.01
405	90 @ 100 61 @ 10	(0.198)
406	23 @ 100	100 @ 1 64 @ 0.1 18 @ 0.01
407	32 @ 100	(0.17)
408	0 @ 100	(0.279)

410	48 @ 100 1 @ 10	67 @ 0.035 47 @ 0.017
411	96 @ 10 81 @ 1	(0.009)
412	31 @ 100	(0.002)
413	0 @ 100	(0.11)
414	0 @ 100	87 @ 1 76 @ 0.1
418	33 @ 100	85 @ 1 52 @ 0.1 53 @ 0.025
419	12 @ 100	(0.1)
420	29 @ 100	(0.323)
421	(0.269)	92 @ 1 81 @ 0.1 38 @ 0.01
422	53 @ 100 82 @ 10 76 @ 1	52 @ 1 37 @ 0.1
423	0 @ 100	87 @ 1 68 @ 0.1 36 @ 0.01
424	7 @ 100	75 @ 1 58 @ 0.1 33 @ 0.01
425	12 @ 100	69 @ 0.1 31 @ 0.01

426	1 @ 100	(0.057)
434	0 @ 100	(0.081)
437	16 @ 100	(0.124)
438	0 @ 100	(0.127)
440	20 @ 100	84 @ 1 59 @ 0.1 22 @ 0.01
442	55 @ 100	90 @ 0.1 56 @ 0.01
443	35 @ 100	86 @ 0.1 74 @ 0.01
444	0 @ 100	83 @ 1 62 @ 0.1 14 @ 10
445	(56.62)	(0.069)
446	0 @ 200	(0.373)
447	0 @ 100	90 @ 1 57 @ 0.1 35 @ 0.01
449	5 @ 200	(0.129)
450	29 @ 100	87 @ 1 40 @ 0.1 22 @ 0.01
451	10 @ 100	43 @ 1 22 @ 0.1

452	14 @ 100	15 @ 1

IL-1ß Induced PGE_2 Production in WISH Cells

Human amnionic WISH cells were grown to 80% confluence in 48 well plates. Following removal of the growth medium and two washings with Gey's Balanced Salt Solutn, 5 ng IL-1ß/ml (UBI, Lake Placid, NY) was added to the cells with or without test compound in DMSO (0.01% v/v) in Neuman-Tytell Serumless Medium (GIBCO, Grand Island, NY). Following an 18 hour incubation to allow for the maximal induction of PGHS-2, the conditioned medium was removed and assayed for PGE_2 content by EIA analysis as described above.

Monocyte U937 (ATCC, Rockville, MD) cells were grown in a similar fashion to the WISH cells. After incubation, the conditioned medium was removed and assayed for Cox-1 content by EIA analysis as described above.

The data illustrating the inhibition of prostaglandin biosynthesis *in vitro* by compounds of this invention is shown in Table 2. U937 values indicate Cox-1 percent inhibition at the particular micromolar dose level while partenthetical values indicate IC_{50} values. WISH cell values indicate percent inhibition at the particular micromolar dose level while parenthetical values indicate IC_{50} values.

Human Whole Platelet Cyclooxygenase-1 Assay (HWCX)

Blood from normal healthy volunteers is collected into tubes containing ACD (acid citrate dextrose) as the anticoagulant. This blood is centrifuged at 175 x g to prepare platelet rich plasma. The platelet rich plasma is then centrifuged at 100 x g to pellet the white blood cells, leaving the platelets in the supernatant. The supernatant is layered on a cushion of 0.7 mL of 10% bovine serum albumin in Tyrodes solution (Gibco; Grand Island, NY) and then centrifuged at 1000 x g. The resulting supernatant from this centrifugation is then removed and 11 mL of Tyrodes solution is added to the remaining pellet of platelets. The platelets are then aliquoted at 120 µl into a 96 well plate. Experimental compounds are added and allowed to pre-incubate for 10 minutes. At the end of this pre-incubation period, the calcium ionophore A23187 is added to a final concentration of 8.8 µM and the incubation is continued for ten minutes. The reaction is stopped by adding cold 6 mM EDTA, the incubation mixture is centrifuged at 220 x g, and the

supernatants are then analyzed for thromboxane using a commercial kit from Cayman Chemical (Ann Arbor, MI).

SEE ATTACHED TABLE

Table 2

Example Numbers	U937 % Inhib. at Dose (μM)	HWPX % Inhib. at Dose (μM)	Wish % Inhib. at Dose (μM)
10		(4.1)	(0.014)
20	33 @ 1		(0.001)
24	(0.19)		(0.007)
43		86 @ 10 9 @ 1	(0.008)
53		78 @ 10 8 @ 1	90 @ 0.1 44 @ 0.01
65			(0.02)
69		(1.14)	(0.02)
72		(25)	(0.072)
75		84 @ 10 0 @ 3	(0.001)
77		(8.8)	(0.126)
85			(0.47)
86			52 @ 1 47 @ 0.01
89	(3.8)	(2.1)	(0.05)
100		(0.13)	(0.02)
102			(0.05)
105		62 @ 1	(0.018)
106		(17.5)	(0.03)
108		(8)	(0.097)
109		(2.693)	(0.018)
119		(0.076)	(0.001)

120		74 @ 3 58 @ 1	(0.025)
121			(0.041)
123		90 @ 1 29 @ .1	(0.001)
126			(0.05)
129			(0.04)
132			100 @ 0.1 36 @ 0.01
140		(0.773)	(0.01)
141		56 @ 0.3	(0.004)
142		(7.53)	(0.088)
143			(0.007)
145		72 @ 1 30 @ .3	(0.009)
146		84 @ 10 46 @ 3	(0.044)
147		84 @ 0.3	(0.029)
148		51 @ 0.3	(0.042)
149		89 @ 10 34 @ 3	(0.03)
152			(0.029)
153		(2.95)	(0.046)
154		81 @ .3 48 @ .1	100 @ 0.1 69 @ 0.01
160		(7.2)	(0.03)
162			(0.034)
165		(1.9)	(0.030)
166		(9.4)	(0.02)
168		47 @ 1	(0.009)
171			90 @ 1 56 @ 0.1
187		(12.6)	(0.015)

189		31 @ 100	(0.041)
190		(9.96)	(0.03)
191			(0.06)
194		(28.09)	(0.069)
198			(0.184)
203			77 @ 1 23 @ 0.1
207			(0.068)
228		(19.6)	(0.086)
241			(0.0474)
243			(0.03)
244		(3.67)	(0.019)
245			(0.046)
246			(0.02)
247		(7.76)	(0.02)
248		82 @ 30 17 @ 10	(0.005)
252			(0.044)
256		(4.7)	(0.028)
261		(34)	(0.099)
271			52 @ 1 15 @ 0.1
278			(0.07)
279			(0.391)
287			(0.16)
317			(0.027)
320		29 @ 3	78 @ .1 15 @ .01
321			50 @ 0.01
322			(0.026)
323			57 @ 0.01
324			(0.047)

325		(2.3)	(0.04)
326			(0.05)
330		(16.7)	(0.005)
335			(0.023)
338		(14.93)	(0.004)
339		(0.393)	(0.026)
343		(0.191)	(0.016)
344			(0.1)
345			(0.03)
349		34 @ 100	(0.041)
352		(5.5)	(6.048)
358			69 @ 1 0 @ 0.1
366		(1.615)	(0.002)
367		50 @ 1 8 @ .3	(0.018)
368		(13.7)	64 @ 0.03 33 @ 0.01
370		(8.4)	(0.02)
374			(0.03)
381		31 @ 30 91 @ 100	(0.075)
385		(2.18)	(0.023)
388		0 @ .3	(0.032)
392		(1.95)	(0.02)
394			(0.019)
396		(12.7)	(0.02)
397		(13.8)	(0.04)
399			82 @ 0.1 39 @ 0.03
400		(0.3)	(0.026)
401		(0.32)	(0.017)

403		(0.902)	(0.018)
404		(0.337)	96 @ 0.1 58 @ 0.01
406		(1.61)	(0.026)
408			(0.029)
410			(0.053)
414			54 @ 1 46 @ 0.1
418		(14.25)	(0.25)
430		34 @ 10 89 @ 100	(0.054)
442			(0.42)
445		100 @ 100 22 @ 1 0	(0.025)
446		(24.4)	(0.02)
449		(40)	(0.089)
450			(0.05)
451		(25.6)	(0.15)
452			56 @ 1 1 @ 0.1

Carrageenan Induced Paw Edema (CPE) in Rats

Hindpaw edema was induced in male rats as described by Winter *et al.*, *Proc. Soc. Exp. Biol. Med.*, **1962**, *111*, 544. Briefly, male Sprague-Dawley rats weighing between 170 and 190 g were administered test compounds orally 1 hour prior to the subplantar injection of 0.1 ml of 1% sodium carrageenan (lambda carrageenan, Sigma Chemical Co., St Louis, MO) into the right hindpaw. Right paw volumes (ml) were measured immediately following injection of carrageenan for baseline volume measurements using a Buxco plethysmograph (Buxco Electronics, Inc., Troy, NY). Three hours after the injection of carrageenan, right paws were remeasured and paw edema calculated for each rat by subtracting the zero time reading from the 3 hour reading. Data are reported as mean percent inhibition +/- SEM. Statistical

significance of results was analyzed by Dunnetts multiple comparison test where $p < 0.05$ was considered statistically significant.

Rat Carrageenan Pleural Inflammati n (CIP) Model

Pleural inflammation was induced in male adrenalectomized Sprague-Dawley rats following the method of Vinegar *et al.*, *Fed. Proc.* **1976,** *35*, 2447-2456. Animals were orally dosed with experimental compounds, 30 minutes prior to the intrapleural injection of 2% lambda carrageenan (Sigma Chemical Co., St. Louis MO). Four hours later the animals were euthanized and the pleural cavities lavaged with ice cold saline. The lavage fluid was then added to two volumes of ice cold methanol (final methanol concentration 66%) to lyse cells and precipitate protein. Eicosanoids were determined by EIA as described above.

The data illustrating the inhibition of prostaglandin biosynthesis *in vivo* by the compounds of this invention is shown in Table 3. Values reported are percent inhibition at 10 milligrams per kilogram body weight.

Carrageenan induced air pouch prostaglandin biosynthesis model (CAP)

Air pouches are formed in the backs of male Sprague Dawley rats by injecting 20 mL of sterile air on day 0. Three days later the pouch was reinflated with an additional 10 mL of sterile air. On day 7, 1 mL of saline containing 0.2 % lambda carrageenan (Sigma Chemical Co.) is injected into the pouch to induce the inflammatory reaction that is characterized by the release of prostaglandins. Test compounds are dosed at 0.1 to 10 mg/kg 30 minutes prior to carrageenan. Four hours after the carrageenan injection the pouch is lavaged and levels of prostaglandins are determined by enzyme immuno-assay using commercially available kits. Percent inhibitions are calculated by comparing the response in animals which have received vehicle to those which received compound. Values for Cox-2 inhibition that are parenthetical indicate ED_{50} values.

The data illustrating the inhibition of prostaglandin biosynthesis *in vivo* by the compounds of this invention is shown in Table 3. Values reported are percent inhibition at 10 milligrams per kilogram body weight for CIP and CPE tests and at 3 milligrams per kilogram body weight for CAP testing.

See attached table

Table 3

Example Numbers	CIP % Inhib. @ 10 mpk	CPE % Inhib. @ 10 mpk	CAP % Inhib. @ 3 mpk
10	44		
12	42	25	
34	36	31	
54	31	30	
58	42	14	67
62	57	21	
66	59	7	0
67	40 @ 3mpk		
68	64	40.3	
69	61	45.5 $ED_{30} = 5.4$	87
72			
73		46	29
74	46.5	18	34
77	51	21	
80	60	28.5	91
89	68.3 $ED_{50} = 3.4$	45.5	94
106			47
109		13	71
112		21	42.5
119	82	27	76
120	5	11	
121	19	8	
123			23
143			59
153			51

160	56	35	
166	40		59
168	0	.6	
180	34.5		
182	59	27	98
185	59	20	53
187	51	28	30
190	60	28	71
205			54
226		21	40.5
243			7
245			47
246			48
248			49
256			47
257			60
261		28	79
330			4.5
335			45
339		43	90.5 ED_{50} = 0.58
346			49.5
347		27	66.5
349			63
351/64			0
352			89 ED_{50} = 5.0
353/63			0
361			65
366			63 ED_{50} = 1.5
367			48

375		47	91 $ED_{50} = 0.30$
376		17	77.5
378			59
384/33	51	15	51
385			65
388		28	80
390			60
391			61
392			60
394			70
395			71
396		23	85
397			70
400	65	41	95
403		43	68.5 $ED_{50} = 0.35$
405			53
406		23	66.5
407			61
419			48
427			78
445		15	73
446		44	92 $ED_{50} = 0.5$
449		23	76 $ED_{50} = 1.8$
450			86
451			80.5 $ED_{50} = 1$
452			71

Pharmaceutical C mpositions

The present invention also provides pharmaceutical compositions which comprise compounds of the present invention formulated together with one or more non-toxic pharmaceutically acceptable carriers. The pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a compound of the present invention formulated together with one or more pharmaceutically acceptable carriers. As used herein, the term "pharmaceutically acceptable carrier" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the procedures and judgements well known to one skilled in the art. The pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, or as an oral or nasal spray.

The compounds of the present invention may be potentially useful in the treatment of several illness or disease states such as inflammatory diseases, dysmennorhea, asthma, premature labor, adhesions and in particular pelvic adhesions, osteoporosis, and ankylosing spondolitis. Current Drugs Ltd, ID Patent Fast Alert, AG16, May 9, 1997.

The compounds of the present invention may also be potentially useful in the treatment of cancers, and in particular, colon cancer. Proc. Natl. Acad. Sci., 94, pp. 3336-3340, 1997.

The compounds of the present invention may be useful by providing a pharmaceutical composition for inhibiting prostaglandin biosynthesis comprising a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt, ester, or prodrug thereof, and a pharmaceutrically acceptable carrier.

The compounds of the present invention may be useful by providing a pharmaceutical composition for inhibiting prostaglandin biosynthesis comprising a therapeutically effective amount of a compound of formula II or a pharmaceutically acceptable salt, ester, or prodrug thereof, and a pharmaceutrically acceptable carrier.

The compounds of the present invention may be useful by providing a pharmaceutical composition for inhibiting prostaglandin biosynthesis comprising a therapeutically effective amount of a compound of formula III or a pharmaceutically acceptable salt, ester, or prodrug thereof, and a pharmaceutrically acceptable carrier.

In addition, the compounds of the present invention may be useful by providing a method for inhibiting prostaglandin biosynthesis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt, ester, or prodrug thereof.

The compounds of the present invention may be useful by providing a method for inhibiting prostaglandin biosynthesis comprising administering to a mammal in need of such treatment a therapeutically effective amount a compound of formula II or a pharmaceutically acceptable salt, ester, or prodrug thereof.

The compounds of the present invention may be useful by providing a method for inhibiting prostaglandin biosynthesis comprising administering to a mammal in need of such treatment a therapeutically effective amount compound of formula III or a pharmaceutically acceptable salt, ester, or prodrug thereof.

In addition, the compounds of the present invention may be useful by providing a method for treating pain, fever, inflamation, rheumatoid arthritis, osteoarthritis, adhesions, and cancer comprising administering to a mammal in need of such teratment a therapeutically effective amount of a compound of formula I.

In addition, the compounds of the present invention may be useful by providing a method for treating pain, fever, inflamation, rheumatoid arthritis,

osteoarthritis, adhesions, and cancer comprising administering to a mammal in need of such teratment a therapeutically effective amount of a compound of formula II.

In addition, the compounds of the present invention may be useful by providing a method for treating pain, fever, inflamation, rheumatoid arthritis, osteoarthritis, adhesions, and cancer comprising administering to a mammal in need of such teratment a therapeutically effective amount of a compound of formula III.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (such as, for example, cottonseed, groundnut, corn, germ, olive, castor, sesame oils, and the like), glycerol, tetrahydrofurfuryl alcohol, poly-ethyl-ene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Injectable preparations, such as, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, such as, for example, a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, isotonic sodium chloride solution, and the like. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectable preparations.

The injectable formulations can be sterilized by any method known in the art, such as, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can

be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microencapsulated matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides) Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and thus melt in the rectum or vaginal cavity and release the active compound.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is usually mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as, for example, sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as, for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as, for example, glycerol, d) disintegrating agents such as, for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as, for example, paraffin, f) absorption accelerators such as, for example, quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as, for example, kaolin and bentonite clay, and) lubricants such

as, for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients such as, for example, lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using excipients such as, for example, lactose or milk sugar as well as high molecular weight polethylene glycols and the like.

The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulation art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as, for example, sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as, for example, magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients such as, for example, animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, poly-

ethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to the compounds of this invention, excipients such as, for example, lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in a suitable medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

According to the methods of treatment of the present invention, a patient, such as a human or mammal, is treated by administering to the patient a therapeutically effective amount of a compound of the invention, in such amounts and for such time as is necessary to achieve the desired result. By a "therapeutically effective amount" of a compound of the invention is meant a sufficient amount of the compound to provide the relief desired, at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

The total daily dose of the compounds of this invention administered to a human or other mammal in single or in divided doses can be in amounts, for example, from 0.001 to about 1000 mg/kg body weight daily or more preferably from about 0.1 to about 100 mg/kg body weight for oral administration or 0.01 to about 10 mg/kg for

parenteral administration daily. Single dose compositions may contain such amounts or submultiples thereof to make up the daily dose.

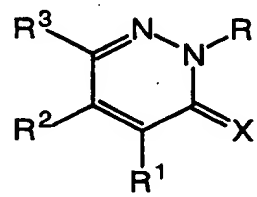
The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

The reagents required for the synthesis of the compounds of the invention are readily available from a number of commercial sources such as Aldrich Chemical Co. (Milwaukee, WI, USA); Sigma Chemical Co. (St. Louis, MO, USA); and Fluka Chemical Corp. (Ronkonkoma, NY, USA); Alfa Aesar (Ward Hill, MA 01835-9953); Eastman Chemical Company (Rochester, New York 14652-3512); Lancaster Synthesis Inc. (Windham, NH 03087-9977); Spectrum Chemical Manufacturing Corp. (Janssen Chemical) (New Brunswick, NJ 08901); Pfaltz and Bauer (Waterbury, CT. 06708). Compounds which are not commercially available can be prepared by employing known methods from the chemical literature.

CLAIMS

We Caim:

1. A compound of formula I:



I

where

X is selected from the group consisting of O, S, NR^4, N-OR^a, and N-NR^bR^c, wherein R^4 is selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, heterocyclic, heterocyclic alkyl, and arylalkyl; and R^a, R^b, and R^c are independently selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, aryl, and arylalkyl;

R is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkylcarbonylalkyl, alkylsulfonylalkyl, alkylsulfonylarylalkyl, alkoxy, alkoxyalkyl, carboxy, carboxyalkyl, cyanoalkyl, haloalkyl, haloalkenyl, haloalkynyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, arylhaloalkyl, arylhydroxyalkyl, aryloxy, aryloxyhydroxyalkyl, aryloxyhaloalkyl, arylcarbonylalkyl, haloalkoxyhydroxyalkyl, heterocyclic, heterocyclic alkyl, heterocyclic alkoxy, heterocyclic oxy, $-C(O)R^5$, $-(CH_2)_nC(O)R^5$, $-R^6-R^7$, $-(CH_2)_nCH(OH)R^5$, $-(CH_2)_nCH(OR^d)R^5$, $-(CH_2)_nC(NOR^d)R^5$, $-(CH_2)_nC(NR^d)R^5$, $-(CH_2)_nCH(NOR^d)R^5$, $-(CH_2)_nCH(NR^dR^e)R^5$, $-(CH_2)_nC{\equiv}C-R^7$, $-(CH_2)_n[CH(CX'_3)]_m-(CH_2)_n-CX'_3$, $-(CH_2)_n(C X'_2)_m-(CH_2)_n-CX'_3$, $-(CH_2)_n[CH(CX'_3)]_m-(CH_2)_n-R^8$, $-(CH_2)_n(C X'_2)_m-(CH_2)_n R^8$, $-(CH_2)_n(CHX')_m-(CH_2)_n - CX'_3$, $-(CH_2)_n(CHX')_m-(CH_2)_n -R^8$, and $-(CH_2)_n-R^{20}$,

wherein R^5 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, haloalkenyl, haloalkynyl, heterocyclic, and heterocyclic alkyl;

wherein R^6 is alkylene or alkenylene, or halo-substituted alkylene halo-substituted alkenylene;

R^7 and R^8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclic, and heterocyclic alkyl;

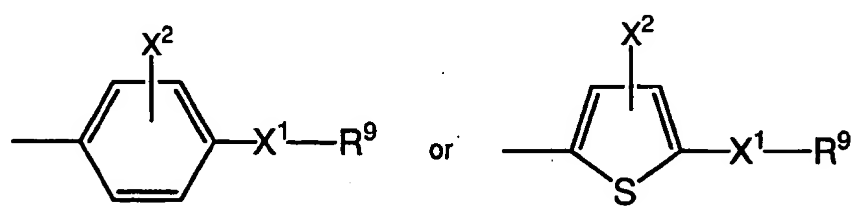
R^{20} is selected from the group consisting of alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkenyl, aryl, heterocyclic, and heterocyclic alkyl;

R^d and R^e are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclic, and heterocyclic alkyl;

X' is halogen;

n is from 0 to about 10, and m is 0 to about 5;

at least one of R^1, R^2 and R^3 is



where X^1 is selected from the group consisting of $-SO_2-$, $-SO(NR^{10})-$, $-SO-$, $-SeO_2-$, $PO(OR^{11})-$, and $-PO(NR^{12}R^{13})-$,

R^9 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, amino, $-NHNH_2$, $-N{=}CH(N\ R^{10}R^{11})$, dialkylamino, alkoxy, thiol, alkylthiol, protecting groups, and protecting groups attached to X^1 by an alkylene;

X^2 is selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, and alkynyl;

R^{10}, R^{11}, R^{12}, and R^{13} are independently selected from the group consisting of hydrogen, alkyl, and cycloalkyl, or R^{12} and R^{13} can be taken together, with the nitrogen to which they are attached, to form a heterocyclic ring having from 3 to 6 atoms.

The remaining two of the groups of R^1, R^2, and R^3, are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, halogen, alkyl, alkenyl, alkynyl, alkylamino, alkenyloxy, alkylthio,

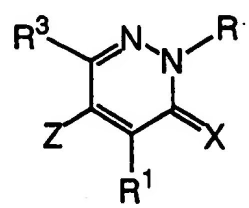
alkylthioalkoxy, alkoxy, alkoxyalkyl, alkoxyalkylamino, alkoxyalkoxy, amido, amidoalkyl, haloalkyl, haloalkenyloxy, haloalkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkenylalkoxy, cycloalkylalkoxy, cycloalkylalkylamino, cycloalkylamino, cycloalkyloxy, cycloalkylidenealkyl, amino, aminocarbonyl, aminoalkoxy, aminocarbonylalkyl, alkylaminoaryloxy, dialkylamino, dialkylaminoaryloxy, arylamino, arylalkylamino, diarylamino, aryl, arylalkyl, arylalkylthio, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, heterocyclic, heterocyclic alkyl, heterocyclic(alkyl) amino, heterocyclic alkoxy, heterocyclic amino, heterocyclic oxy, heterocyclic thio, hydroxy, hydroxyalkyl, hydroxyalkylamino, hydroxyalkoxy,hydroxyalkylthio, mercaptoalkoxy, oxoalkoxy, cyano, nitro, and -Y-R^{14}, wherein Y is selected from the group consisting of -O-, -S-, -C(R^{16}) (R^{17})-, -C(O)N$R^{21}R^{22}$-, -C(O)-, -C(O)O-, -NH-, -NC(O)-, -N=C $R^{21}R^{22}$, N- $R^{21}R^{22}$, and -NR^{19}-. R^{14} is selected from the group consisting of hydrogen, halogen, alkyl, alkoxyalkyl, alkylthioalkyl, alkenyl, alkynyl, hydroxy, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, cycloalkenyl, amino, cyano, aryl, arylalkyl, heterocyclic, and heterocyclic(alkyl),

R^{16}, R^{17}, and R^{19} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano; and

R^{21} and R^{22} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano;

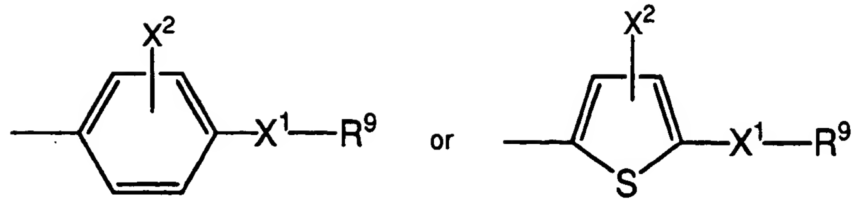
or a pharmaceutically acceptable salt, ester, or prodrug thereof.

2. A compound having the formula II:



II

wherein Z is a group having the formula:



where X^1 is selected from the group consisting of $-SO_2-$, $-SO-$, $-SeO_2-$,$SO(NR^{10})-$, and R^9 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, amino, $-NHNH_2$, dialkylamino, alkoxy, thiol, alkylthiol, protecting groups, and protecting groups attached to X^1 by an alkylene;

R^{10} is selected from the group consisting of hydrogen, alkyl, and cycloalkyl;

X^2 is selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, and alkynyl;

R is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkylcarbonylalkyl, alkylsulfonylalkyl, alkylsulfonylarylalkyl, alkoxy, alkoxyalkyl, carboxy, carboxyalkyl, cyanoalkyl, haloalkyl, haloalkenyl, haloalkynyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, arylhaloalkyl, arylhydroxyalkyl, aryloxy, aryloxyhydroxyalkyl, aryloxyhaloalkyl, arylcarbonylalkyl, haloalkoxyhydroxyalkyl, heterocyclic, heterocyclic alkyl, heterocyclic alkoxy, heterocyclic oxy, $-C(O)R^5$, $-(CH_2)_nC(O)R^5$, $-R^6-R^7$, $-(CH_2)_nCH(OH)R^5$, $-(CH_2)_nCH(OR^d)R^5$, $-(CH_2)_nC(NOR^d)R^5$, $-(CH_2)_nC(NR^d)R^5$, $-(CH_2)_nCH(NOR^d)R^5$, $-(CH_2)_nCH(NR^dR^e)R^5$, $-(CH_2)_nC{\equiv}C-R^7$, $-(CH_2)_n[CH(CX'_3)]_m-(CH_2)_n-CX'_3$, $-(CH_2)_n(C X'_2)_m-(CH_2)_n -CX'_3$, $-(CH_2)_n[CH(CX'_3)]_m-(CH_2)_n -R^8$, $-(CH_2)_n(C X'_2)_m-(CH_2)_n R^8$, $-(CH_2)_n(CHX')_m-(CH_2)_n - CX'_3$, $-(CH_2)_n(CHX')_m-(CH_2)_n -R^8$, and $-(CH_2)_n-R^{20}$,

wherein R^5 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, haloalkenyl, haloalkynyl, heterocyclic, and heterocyclic alkyl;

wherein R^6 is alkylene or alkenylene, or halo-substituted alkylene halo-substituted alkenylene;

R^7 and R^8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclic, and heterocyclic alkyl;

R^{20} is selected from the group consisting of alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkenyl, aryl, heterocyclic, and heterocyclic alkyl;

R^d and R^e are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclic, and heterocyclic alkyl;

X' is halogen;

n is from 0 to about 10, and m is 0 to about 5;

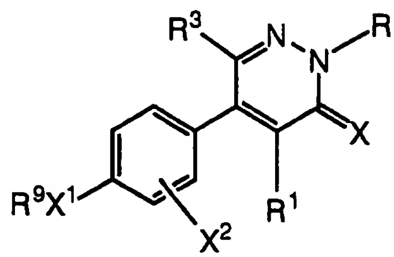
R^1, and R^3 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, halogen, alkyl, alkenyl, alkynyl, alkylamino, alkenyloxy, alkylthio, alkylthioalkoxy, alkoxy, alkoxyalkyl, alkoxyalkylamino, alkoxyalkoxy, amido, amidoalkyl, haloalkyl, halolkenyloxy, haloalkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkenylalkoxy, cycloalkylalkoxy, cycloalkylalkylamino, cycloalkylamino, cycloalkyloxy, amino, aminocarbonyl, aminoalkoxy, aminocarbonylalkyl, alkylaminoaryloxy, dialkylamino, dialkylaminoaryloxy, arylamino, arylalkylamino, diarylamino, aryl, arylalkyl, arylalkylthio, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, heterocyclic, heterocyclic alkyl, heterocyclic(alkyl) amino, heterocyclic alkoxy, heterocyclic amino, heterocyclic oxy, heterocyclic thio, hydroxy, hydroxyalkyl, hydroxyalkylamino, hydroxyalkoxy, mercaptoalkoxy, oxoalkoxy, cyano, nitro, and -Y-R^{14}, wherein Y is selected from the group consisting of -O-, -S-, -C(R^{16})(R^{17})-, -C(O)N$R^{21}R^{22}$-, -C(O)-, -C(O)O-, -NH-, -NC(O)-, -N=C $R^{21}R^{22}$, N-$R^{21}R^{22}$, and -NR^{19}-. R^{14} is selected from the group consisting of hydrogen, halogen, alkyl, alkoxyalkyl, alkylthioalkyl, alkenyl, alkynyl, hydroxy, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, cycloalkenyl, amino, cyano, aryl, arylalkyl, heterocyclic, and heterocyclic(alkyl),

R^{16}, R^{17}, and R^{19} are independently selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano; and

R^{21} and R^{22} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

3. A compound having the formula **III**:



III

wherein X, X^1, X^2, R, R^1, R^3, and R^9 are as defined in claim 1; or a pharmaceutically acceptable salt, ester, or prodrug thereof.

4. A compound of claim 3 wherein X^1 is selected from the group consisting of $-SO_2-$, $-SO-$, $-SeO_2-$, and $-SO(NR^{10})-$, and R^9 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, amino, alkylamino, or dialkylamino;

X^2 is selected from the group consisting of hydrogen and halogen;

X is selected from the group consisting of O, S, NR^4, $N\text{-}OR^a$, and $N\text{-}NR^bR^c$, wherein R^4 is selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, heterocyclic, heterocyclic alkyl, and arylalkyl; and R^a, R^b, and R^c.are independently selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, aryl, and arylalkyl;

R is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkylcarbonylalkyl, alkylsulfonylalkyl, alkylsulfonylarylalkyl, carboxyalkyl, cyanoalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkenyl, arylalkynyl, heterocyclic, heterocyclic alkyl, arylalkyl, $-(CH_2)_nC(O)R^5$, $-(CH_2)_nC{\equiv}C-R^7$, $-(CH_2)_n[CH(CX'_3)]_m(CH_2)_n-R^8$, and $-(CH_2)_n-R^{20}$;

wherein R^5 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, heterocyclic, and heterocyclic alkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, heterocyclic, and heterocyclic alkyl,

R^{20} is selected from the group consisting of alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkenyl, aryl, heterocyclic, and heterocyclic alkyl;

X' is halogen;

n is from 0 to about 10, m is from 0 to about 5;

R^1 and R^3 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, halogen, alkyl, alkenyl, alkynyl, alkoxy, alkenyloxy, alkoxyalkyl, amido, amidoalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, amino, aminocarbonyl, aminocarbonylalkyl, alkylamino, dialkylamino, arylamino, arylalkylamino, diarylamino, aryl, aryloxy, heterocyclic, heterocyclic alkyl, cyano, nitro, and -Y-R^{14}, wherein Y is selected from the group consisting of, -O-, -S-, -C(R^{16}) (R^{17})-, -C(O)N$R^{21}R^{22}$-, -C(O)-, -C(O)O-, -NH-, -NC(O)-, -N=C $R^{21}R^{22}$, N- $R^{21}R^{22}$, and -NR^{19}-. R^{14} is selected from the group consisting of hydrogen, halogen, alkyl, alkoxyalkyl, alkylthioalkyl, alkenyl, alkynyl, hydroxy, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, cycloalkenyl, amino, cyano, aryl, arylalkyl, heterocyclic, and heterocyclic(alkyl),

R^{16}, R^{17}, and R^{19} are independently selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano; and

R^{21} and R^{22} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

5. A compound of claim 3 wherein X^1 is selected from the group consisting of -SO_2-, -SO-, -SeO_2-, and -SO(NR^{10})-, and R^9 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, amino, alkylamino, or dialkylamino;

X^2 is selected from the group consisting of hydrogen and halogen;

X is selected from the group consisting of O, S, NR^4, N-OR^a, and N-NR^bR^c, wherein R^4 is selected from the group consisting of alkyl, alkenyl, cyclo-

alkyl, cycloalkenyl, cycloalkylalkyl, alkylcycloalkenyl, aryl, heterocyclic, and arylalkyl; and R^a, R^b, and R^c.are independently selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, aryl, and arylalkyl;

R is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkylcarbonylalkyl, alkylsulfonylalkyl, alkylsulfonylarylalkyl, carboxyalkyl, cyanoalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkenyl, arylalkynyl, heterocyclic, heterocyclic alkyl, arylalkyl, $-(CH_2)_nC(O)R^5$, and $-(CH_2)n-R^{20}$;

wherein R^5 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, heterocyclic, and heterocyclic alkyl;

R^{20} is selected from the group consisting of alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkenyl, aryl, heterocyclic, and heterocyclic alkyl;

n is from 0 to about 10;

$R^1$and R^3 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, halogen, alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, alkylthioalkyl, aryloxyalkyl, arylthioalkyl, amido, amidoalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, amino, aminocarbonyl, aminocarbonylalkyl, alkylamino, alkylaminoalkyl, dialkylamino, arylamino, arylalkylamino, diarylamino, aryl, heterocyclic, heterocyclic(alkyl), cyano, nitro, and $-Y-R^{14}$, wherein Y is selected from the group consisting of, -O-, -S-, $-C(R^{16}) (R^{17})-$, $-C(O)NR^{21}R^{22}-$, -C(O)-, -C(O)O-, -NH-, -NC(O)-, and $-NR^{19}-$. R^{14} is selected from the group consisting of hydrogen, halogen, alkyl, alkoxyalkyl, alkylthioalkyl, alkenyl, alkynyl, hydroxy, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, cycloalkenyl, amino, cyano, aryl, arylalkyl, heterocyclic, and heterocyclic(alkyl), and

R^{16}, R^{17}, and R^{19} are independently selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano;

R^{21} and R^{22} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

6. A compound of claim 3 wherein X^1 is selected from the group consisting of $-SO_2-$, -SO-, $-SeO_2-$, and-SO(NR^{10})-, and R^9 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, amino, alkylamino, or dialkylamino;

X^2 is selected from the group consisting of hydrogen and halogen;

X is selected from the group consisting of O, S, NR^4, N-OR^a, and N-NR^bR^c, wherein R^4 is selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, alkylcycloalkenyl, aryl, heterocyclic, and arylalkyl; and R^a, R^b, and R^c.are independently selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, aryl, and arylalkyl;

R is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkylcarbonylalkyl, alkylsulfonylalkyl, alkylsulfonylarylalkyl, carboxyalkyl, cyanoalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkenyl, arylalkynyl, heterocyclic, heterocyclic alkyl, arylalkyl, and $-(CH_2)_nC(O)R^5$,;

wherein R^5 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, heterocyclic, and heterocyclic alkyl; and

n is from 0 to about 10;

$R^1$and R^3 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, halogen, alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, alkylthioalkyl, aryloxyalkyl, arylthioalkyl, amido, amidoalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, amino, aminocarbonyl, aminocarbonylalkyl, alkylamino, alkylaminoalkyl, dialkylamino, arylamino, arylalkylamino, diarylamino, aryl, heterocyclic, heterocyclic(alkyl), cyano, nitro, and -Y-R^{14}, wherein Y is selected from the group consisting of, -O-, -S-, -C(R^{16}) (R^{17})-, -C(O)$NR^{21}R^{22}$-, -C(O)-, -C(O)O-, -NH-, -NC(O)-, and -NR^{19}-. R^{14} is selected from the group consisting of hydrogen, halogen, alkyl, alkoxyalkyl, alkylthioalkyl, alkenyl, alkynyl, hydroxy, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, cycloalkenyl, amino, cyano, aryl, arylalkyl, heterocyclic, and heterocyclic(alkyl);

R^{15}, R^{16}, R^{17}, and R^{19} are independently selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl or cyano;

R^{21} and R^{22} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

7. A compound of claim 3 wherein X^1 is selected from the group consisting of $-SO_2-$, -SO-, $-SeO_2-$, and $-SO(NR^{10})-$, and R^9 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, amino, alkylamino, or dialkylamino;

X^2 is selected from the group consisting of hydrogen and halogen;

X is selected from the group consisting of O, S, NR^4, $N\text{-}OR^a$, and $N\text{-}NR^bR^c$, wherein R^4 is selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, alkylcycloalkenyl, aryl, heterocyclic, and arylalkyl; and R^a, R^b, and R^c.are independently selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, aryl, and arylalkyl;

R is selected from alkyl, haloalkyl, aryl, heterocyclic, heterocyclic alkyl, and $-(CH_2)n-R^{20}$ where is R^{20} is substituted and unsubstituted aryl wherein the substituted aryl compounds are substituted with halogen;

n is from 0 to about 10;

R^1 is selected from the group consisting of alkoxy, alkenyloxy, hydroxyalkoxy, aryloxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, and $-Y-R^{14}$, wherein Y is selected from the group consisting of, -O-, -S-, $-C(R^{16})(R^{17})-$, -C(O)-, -C(O)O-, -NH-, -NC(O)-, and $-NR^{19}-$. R^{14} is selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkynyl, hydroxy, cycloalkyl, cycloalkenyl, amino, cyano, aryl, arylalkyl, heterocyclic, and heterocyclic alkyl,

R^3 is hydrogen;

R^{15}, R^{16}, R^{17}, and R^{19} are independently selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano; and

R^{21} and R^{22} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, or cyano;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

8. A compound of claim 3 wherein X^1 is selected from the group consisting of $-SO_2-$, -SO-, and $-SO(NR^{10})-$, and R^9 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, amino, alkylamino, or dialkylamino;

X^2 is selected from the group consisting of hydrogen and halogen;

X is selected from the group consisting of O, S, NR^4, $N-OR^a$, and $N-NR^bR^c$, wherein R^4 is selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, alkylcycloalkenyl, aryl, heterocyclic, and arylalkyl; and R^a, R^b, and R^c.are independently selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, aryl, and arylalkyl;

R is selected from alkyl, haloalkyl, aryl, heterocyclic, heterocyclic alkyl, and $-(CH_2)n-R^{20}$ where is R^{20} is substituted and unsubstituted aryl wherein the substituted aryl compounds are substituted with halogen;

n is from 0 to about 10;

R^1 is selected from the group consisting of alkoxy, alkenyloxy, hydroxyalkoxy, aryloxy, aryl, arylalkyl, heterocyclic, and heterocyclic alkyl; and

R^3 is hydrogen;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

9. A compound of claim 3 wherein X^1 is $-SO_2-$ and and R^9 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, amino, alkylamino, or dialkylamino;

X^2 is selected from the group consisting of hydrogen and halogen;

X is selected from the group consisting of O, S, NR^4, $N-OR^a$, and $N-NR^bR^c$, wherein R^4 is selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, alkylcycloalkenyl, aryl, heterocyclic, and arylalkyl; and R^a, R^b, and R^c.are independently selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, aryl, and arylalkyl;

R is selected from haloalkyl, aryl, heterocyclic, heterocyclic alkyl, and $-(CH_2)n-R^{20}$ where is R^{20} is substituted and unsubstituted aryl wherein the substituted aryl compounds are substituted with halogen;

n is from 0 to about 10;

R^1 is selected from the group consisting of unsubstituted aryl, and substituted aryl with one, two, or three substituents selected from the group consisting of fluorine and chlorine including, but not limited to, *p*-chlorophenyl, *p*-fluorophenyl, 3,4-dichlorophenyl, 3-chloro-4-fluoro-phenyl, and the like; and

R^3 is hydrogen;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

10. A compound of claim 3 wherein X^1 is $-SO_2-$,and R^9 is selected from the group consisting of alkyl and amino;

X^2 is selected from the group consisting of hydrogen and halogen;

X is O;

R is selected from the group consisting of alkyl, alkenyl, alkynyl, haloalkyl, aryl, and arylalkyl;

R^1 is selected from the group consisting of alkoxy, aryl, alkenyloxy, hydroxyalkoxy, haloalkoxy, arylalkyl, alkyl, and aryloxy; and

R^3 is hydrogen;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

11. A compound of claim 3 wherein X^1 is $-SO_2-$, and R^9 is selected from the group consisting of alkyl and amino;

X^2 is selected from hydrogen and fluorine;

R is selected from haloalkyl, aryl, and alkyl;

n is from 0 to about 10;

R^1 is selected from the group consisting of isobutyloxy, isopentyloxy, 1-(3-methyl-3-butenyl)oxy, 2-hydroxy-2-methyl-propyloxy, 3-hydroxy-3-methyl-butyloxy, neopentyloxy, isopentyl, aryloxy including 4-fluorophenoxy, unsubstituted

aryl, and substitued aryl with one, two, or three substituents selected from the group consisting of fluorine and chlorine including, , 4-fluorophenyl, 4-chlorophenyl, 3-chloro-4-fluoro-phenyl4-chloro-3-fluoro-phenyl; and

R^3 is hydrogen;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

12. A compound of claim 3 wherein X^1 is selected from the group consisting of $-SO_2-$, and $-SO(NR^{10})-$, and R^9 is alkyl,

X^2 is selected from the group consisting of hydrogen and fluorine;

X is O;

R is selected from the group consisting of alkyl, alkenyl, alkynyl, haloalkyl, aryl, and arylalkyl;

R^1 is selected from the group consisting of alkoxy, aryl, alkenyloxy, hydroxyalkoxy, alkyl, and aryloxy; and

R^3 is hydrogen;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

13. A compound of claim 3 wherein X^1 is $-SO_2-$, R^9 is amino;

X^2 is selected from the group consisting of hydrogen and fluorine;

X is O;

R is selected from the group consisting of alkyl, alkenyl, alkynyl, haloalkyl, aryl, and arylalkyl;

R^1 is selected from the group consisting of alkoxy, aryl, alkenyloxy, hydroxyalkoxy, alkyl, and aryloxy; and

R^3 is hydrogen;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

14. A compound of claim 3 wherein X^1 is $-SO_2-$, and R^9 is methyl;

X^2 is selected from the group consisting of hydrogen;

X is O;

R is selected from the group consisting t-butyl, 3-chlorophenyl, 3,4-difluorophenyl, 4-fluorophenyl, 4-chloro-3-fluoro-phenyl, 3-chloro-4-fluoro-phenyl, and CF_3CH_2-, ;

R^1 is selected from the group consisting of aryloxy, isobutyloxy, isopentyloxy, 1-(3-methyl-3-butenyl)oxy, 2-hydroxy-2-methyl-propyloxy, 3-hydroxy-3-methyl-butyloxy, neopentyloxy, isopentyl, 4-fluorophenyl, 4-chlorophenyl, 4-chloro-3-fluoro-phenyl,4-fluorophenoxy; and

R^3 is hydrogen;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

15. A compound of claim 3 wherein X^1 is $-SO_2-$, and R^9 is amino;

X^2 is selected from the group consisting of hydrogen;

X is O;

R is selected from the group consisting t-butyl, 3-chlorophenyl, 3,4-difluorophenyl, 4-fluorophenyl, 4-chloro-3-fluoro-phenyl, 3-chloro-4-fluoro-phenyl and CF_3CH_2-, ;

R^1 is selected from the group consisting of aryloxy, isobutyloxy, isopentyloxy, 1-(3-methyl-3-butenyl)oxy, 2-hydroxy-2-methyl-propyloxy, 3-hydroxy-3-methyl-butyloxy, neopentyloxy, isopentyl, 4-fluorophenyl, 4-chlorophenyl, 4-chloro-3-fluoro-phenyl,4-fluorophenoxy; and

R^3 is hydrogen;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

16. A compound according to claim 3, selected from the group consisting of:

2-(2,2,2-Trifluoroethyl)-4-(4-chlorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(3-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3-Chlorophenyl)-4-(3-methyl-3-butenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(2,2,2-Trifluoroethyl)-4-(4-chloro-3-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-fluorophenyl)-4-(4-flurophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(3-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(*t*-Butyl)-4-(3-methylbutoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(*t*-Butyl)-4-(3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(2,2,2-Trifluoroethyl)-4-(2,2-dimethylpropoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(2,2,2-Trifluoroethyl)-4-(2-methylpropoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(3-methylbutoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(3-methylbutyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3-Chlorophenyl)-4-(3-methylbutoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3-Chlorophenyl)-4-(3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(2-methylpropoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3-Chlorophenyl)-4-(2-methylpropoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(3-methylbutoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(2-methylpropoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(2-methylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(2-methylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(4-fluorophenoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;
2-(4-Fluorophenyl)-4-(4-fluorophenoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(2,2,2-Trifluoroethyl)-4-(2,2-dimethylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Chloro-3-fluorophenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(4-fluorophenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)- -4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]- 3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2,4-Bis(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-3(2H)-pyridazinone;

2-(4-fluorophenyl)-4-(4-flurophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone; and

2-(3,4-Difluorophenyl)-4-(2-hydroxy-2-methylpropoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(2-oxopropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(2-methoxy-imino-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

(R)-2-(3,4-Difluorophenyl)-4-(3-hydroxy-2-methylpropoxy)-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone;

(S)- 2-(3,4-Difluorophenyl)-4-(3-hydroxy-2-methylpropoxy)-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone;

(R)-2-(3,4-Difluorophenyl)-4-(3-hydroxy-2-methylpropoxy)-5-[4-(aminosulfonyl)-phenyl]-3(2H)-pyridazinone;

(S)- 2-(3,4-Difluorophenyl)-4-(3-hydroxy-2-methylpropoxy)-5-[4-(aminosulfonyl)-phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(3-oxo-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(3-oxo-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone; and

2,4-Bis(4-Flurophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

17. A compound of claim 16 selected from the group consisting of

2-Phenyl-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-3(2H)-pyridazinone;
2-(2,2,2-Trifluoroethyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-3(2H)-pyridazinone;

2-(2,2,2-Trifluoroethyl)-4-(4-chlorophenyl)-5-(4-methylsulfonylphenyl)-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(2-methylpropoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone; and

2,4-Bis(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-3(2H)-pyridazinone;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

18. A pharmaceutical composition for inhibiting prostaglandin biosynthesis comprising a therapeutically effective amount of the compound of claim 1 and a pharmaceutrically acceptable carrier.

19. A pharmaceutical composition for inhibiting prostaglandin biosynthesis comprising a therapeutically effective amount of the compound of claim 2 and a pharmaceutrically acceptable carrier.

20. A pharmaceutical composition for inhibiting prostaglandin biosynthesis comprising a therapeutically effective amount of the compound of claim 3 and a pharmaceutrically acceptable carrier.

21. A method for inhibiting prostaglandin biosynthesis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of claim 1.

22. A method for inhibiting prostaglandin biosynthesis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of claim 2.

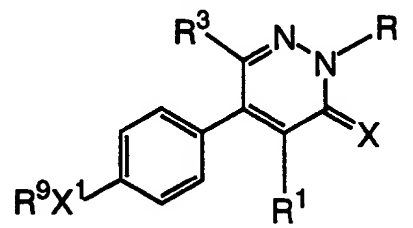
23. A method for inhibiting prostaglandin biosynthesis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of claim 3.

24. A method for treating pain, fever, inflamation, rheumatoid arthritis, osteoarthritis, adhesions, and cancer comprising administering to a therapeutically effective amount of a compound of claim 1.

25. A method for treating pain, fever, inflamation, rheumatoid arthritis, osteoarthritis, adhesions, and cancer comprising administering to a therapeutically effective amount of a compound of claim 2.

26. A method for treating pain, fever, inflamation, rheumatoid arthritis, osteoarthritis, adhesions, and cancer comprising administering to a therapeutically effective amount of a compound of claim 3.

27. A method for the preparation of a compound of claim 3 , or a pharmaceutically acceptable salt, ester, or prodrug thereof having the formula :



III

wherein X, X^1, X^2, R, R^1, R^3, and R^9 are as defined in claim 1;

comprising the step of reacting a compound having formula III, where R is hydrogen, with an alkylating agent.

28. The method according to claim 27 wherein the alkylating agent has the formula R^{99}-Q where Q is a leaving group and R^{99} is selected from the group consisting of methyl, ethyl, 1,1,1-trifluoroethyl, cyclopropylmethyl, 3-(2-methyl)-propenyl, 4-(2-methyl)but-2-enyl, 1,1-dichloropropen-3-yl, 2,2-dimethyl-3-oxo-4-butyl, 2,3,3,4,4,4-hexafluoro-n-buten-1-yl, propargyl, phenylpropargyl, phenyl, phenethyl, 1-phenylpropen-3-yl, benzyl, α-methyl-4-fluorobenzyl, 2,3,4,5,6-pentafluorobenzyl, 4-trifluomethoxyphenacyl, 4-fluorobenzyl, 4-fluorophenyl, 2-trifluoromethylbenzyl, 2,4-difluorobenzyl, 2,4-difluorophenacyl, 4-trifluomethylphenacyl, phenacyl, 4-carboxyphenacyl, 4-chlorophenacyl, 4-cyanophenacyl, 4-diethylaminophenacyl, 3-thienylmethyl, 5-methylthien-2-ylmethyl, 5-chlorothien-2-ylmethyl, 2-benzo[b]thienylmethyl, 3-benzothienacyl, 5-chlorothiazol-2-ylmethyl, 5-methylthiazol-2-ylmethyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, quinolin-2-ylmethyl, and fluoroquinolin-2-ylmethyl.

29. The method according to claim 27 wherein the alkylating agent has the formula R^{99}-Q where Q is a leaving group and R^{99} is selected from the group consisting of methyl, ethyl, 1,1,1-trifluoroethyl, cyclopropylmethyl, 3-(2-methyl)-propenyl, 4-(2-methyl)but-2-enyl, 1,1-dichloropropen-3-yl, 2,3,3,4,4,4-hexafluoro-n-buten-1-yl, propargyl, phenylpropargyl, phenyl, phenethyl, 1-phenylpropen-3-yl, benzyl, α-methyl-4-fluorobenzyl, 2,3,4,5,6-pentafluorobenzyl, 4-trifluomethoxy-phenacyl, 4-fluorobenzyl, 4-fluorophenyl, 2,4-difluorobenzyl, 2,4-difluorophenacyl, 4-trifluomethylphenacyl, phenacyl, 4-carboxyphenacyl, 4-chlorophenacyl, 4-cyanophenacyl, 4-diethylaminophenacyl, 3-thienylmethyl, 5-methylthien-2-yl-methyl, 5-chlorothien-2-ylmethyl, 2-benzo[b]thienylmethyl, and 3-benzothienacyl.

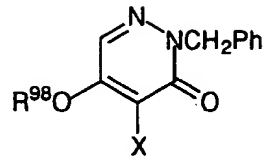
30. The method according to claim 27 wherein the alkylating agent has the formula R^{99}-Q where Q is a leaving group and R^{99} is selected from the group consisting of 1,1,1-trifluoroethyl, 3-(2-methyl)propenyl, 4-(2-methyl)but-2-enyl, 1,1-dichloropropen-3-yl, 2,3,3,4,4,4-hexafluoro-n-buten-1-yl, propargyl, phenyl-propargyl, phenyl, benzyl, α-methyl-4-fluorobenzyl, 2,3,4,5,6-pentafluorobenzyl, 4-fluorobenzyl, 4-fluorophenyl, 2,4-difluorobenzyl, 3-thienylmethyl, 5-methylthien-2-ylmethyl, 5-chlorothien-2-ylmethyl, and 2-benzo[b]thienylmethyl.

31. The method according to claim 27 wherein the alkylating agent has the formula R^{99}-Q where Q is a leaving group and R^{99} is selected from the group consisting of 1,1,1-trifluoroethyl, phenyl, benzyl, α-methyl-4-fluorobenzyl, 4-fluoro-benzyl, 4-fluorophenyl, and 2,4-difluorobenzyl.

32. The method according to claim 27 wherein the alkylating agent has the formula R^{99}-Q where Q is a leaving group and R^{99} is selected from the group consisting of 1,1,1-trifluoroethyl, benzyl, and 4-fluorophenyl.

33. A method for regioselectively preparing a 4,5- substituted pyridazone comprising the steps of

a) reacting a compound with the formula



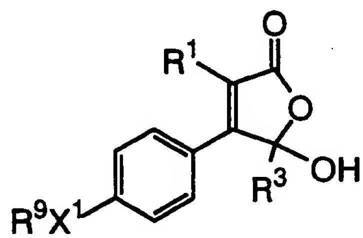
where R is an alkyl or aryl group, and X is a leaving group with a nucleophilic agent to displace the X group;

b) converting the $-OR^{98}$ to a leaving group; and

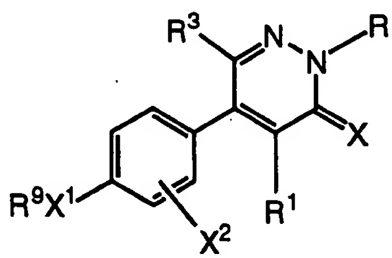
c) reacting the compound with a second nucleophilic agent to provide the 4,5- substituted pyridazone.

34. The method according to claim 33 wherein the benzyl group is removed using a Lewis acid.

35. A method for regioselectivly preparing a 4,5- substituted pyridazone comprising the steps of treating a compound having the formula



with a hydrazine having the formula $RNHNH_2$ to furnish the pyridazone having the formula:



III

wherein X, X^1, X^2, R, R^1, R^3, and R^9 are as defined in claim 1; or a pharmaceutically acceptable salt, ester, or prodrug thereof.

INTERNATIONAL SEARCH REPORT

Intern .al Application No
PCT/US 98/16479

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D237/14 C07D401/06 C07D403/06 C07D237/18 C07D409/06
C07D413/06 C07D405/06 A61K31/50 C07F11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 714 895 A (F. HOFFMANN-LA ROCHE AG) 5 June 1996 see claims 1-23	1-35
A	EP 0 711 759 A (ROHM AND HAAS COMPANY) 15 May 1996 see claims 1-8	1-35
A	WO 88 09675 A (MEDICIS CORPORATION) 15 December 1988 see claims 3,4	1-35

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 October 1998	15/10/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Herz, C

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern. ıal Application No
PCT/US 98/16479

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	D. E. GRISWOLD, J. L. ADAMS: "Constitutive Cyclooxygenase (COX-1) and Inducible Cyclooxygenase (COX-2): Rationale for Selective Inhibition and Progress to Date" MEDICINAL RESEARCH REVIEWS, vol. 16, no. 2, 1996, pages 181-206, XP002040558 -----	1-35

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. al Application No
PCT/US 98/16479

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 714895 A	05-06-1996	US 5622948 A	22-04-1997
		AU 3906295 A	06-06-1996
		BR 9505610 A	16-09-1997
		CA 2163490 A	02-06-1996
		CN 1132206 A	02-10-1996
		CZ 9503169 A	12-06-1996
		FI 955783 A	02-06-1996
		HU 75117 A	28-04-1997
		JP 8208639 A	13-08-1996
		NO 954878 A	03-06-1996
		PL 311536 A	10-06-1996
		SG 33609 A	18-10-1996
		ZA 9510027 A	03-06-1996
EP 711759 A	15-05-1996	AU 691673 B	21-05-1998
		AU 3666695 A	23-05-1996
		BR 9505160 A	21-10-1997
		CA 2162775 A	15-05-1996
		CN 1128758 A	14-08-1996
		CZ 9502989 A	15-05-1996
		HU 72912 A	28-06-1996
		JP 8225540 A	03-09-1996
		NZ 280413 A	26-07-1996
		PL 311361 A	27-05-1996
		ZA 9509612 A	29-05-1996
WO 8809675 A	15-12-1988	NONE	